EVALUATION, CONTROL, AND PREDICTION OF DRUG DIFFUSION THROUGH POLYMERIC MEMBRANES

By

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DEDICATION

To my wife,

Mrunal,

whose patience and help made this accomplishment possible

and to my parents,

Mr. and Mrs. Bhaurao H. Chemburkar,

whose encouragement has been a source of unending energy to me.

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INTRODUCTION

The differential transport of substances in solution through membranes has been used for separations based on differences in molecular weights (1-6). The selectivity of membranes to penetrants has been used to enrich or separate mixtures of gases (7, 8, 9) based on the basic information obtained on the transport of gases and water vapors through membranes (10). The models of transport processes in the artificial membranes are being used to explain the possible mechanisms for the passage of nutrients and drugs across a succession of membranes in the living organism (11-15).

However, fundamental studies on the diffusion of drugs through artificial membranes to formulate optimal dosage forms are scarce and mostly qualitative in nature (16, 17, 18). Basic and quantitative information is needed to predict the transference of drugs in solution through membranes to provide proper dosage forms based on known values of release of drugs through these membranes.

The purposes of this investigation were to determine and quantify the basic factors that influence the diffusion of drugs through synthetic polymeric membranes. The rates of diffusion were to be correlated with all measurable physical and chemical parameters that could be used to predict the diffusivities of drugs. Ultimately it was planned to test the predicted *in vitro* diffusion of drugs from pharmaceutically proper dosage forms.

HISTORICAL

A membrane is an imperfect barrier separating two fluids, whether gases or liquids. Membrane technology (19) and the application of polymeric materials in the medical and health related professions (20, 21) have been discussed in recent fine reviews.

Diffusion is defined as the tendency for molecules to migrate from a region of high concentration to a region of lower concentration and is a direct result of molecular movement. Dialysis is a term applied to the use of membranes for the separation of particles of colloidal dimensions from the molecules of suspending liquid and is a consequence of diffusion (22).

Dialysis, as observed in transport through cellophane and animal membranes and parchment papers (23, 24, 25), is due to sieve action. Such membranes may be considered as heterogeneous barriers in the sense that they possess pores. The transport is generally a measure of the probability of a solvated molecule entering and diffusing through the pores. There is little selectivity in the separation of two closely related molecules except when their size is approximately that of the size of the pore (26). In general, the solvent as well as the solute is transported; membranes which allow salt transport are permeable to water (27).

Dialysis, where a membrane acts as a barrier to free diffusion of a substance in an isotropic medium, is largely dependent on the molecular weight of the diffusate and the viscosity of the solvent. The Sutherland and Einstein equation (28) for spherical colloidal particles is (Appendix C-I)

$$D = (RT/6\pi n\ N)\ (4\pi N/3\ M\ \bar{v})^{1/3} \qquad \text{(Eq. 1)}$$

where D is the diffusion coefficient, R is the molar gas constant, T is the absolute temperature, n is the viscosity of the solvent, N is the Avogadro's number, M is the molecular weight and $\bar{v}$ is the partial specific volume of the solute. An empirical relation correlating diffusion constant, molecular weight and viscosity is (29)

$$D = 7.4 \times 10^{-8}\ (XM)^{0.5}\ \ T/n\ \bar{v}^{\ 0.6} \qquad \text{(Eq. 2)}$$

where X is an association parameter defining the effective molecular weight of the solvent with respect to the diffusing species (for water X = 2.6).

Dialysis has been used for the separation of the components of blood (26, 30), the transfer of macromolecules in an artificial kidney (31), the fractionation of high polymers (25), the correlation of molecular size and structure with transport rates (1-6) and the determination of the binding of drugs and chemicals to proteins and macromolecules (32). Ion-exchange resins have been used extensively for the separation of charged particles or molecules (33-37). Electrodialysis, where electromotive force is used as the driving force for the separation of ionic solutes, has been used for the recovery of salts from sea water (38, 39, 40), the recovery of acids from spent acid solutions (41), and the partial demineralization of milk and whey (42).

Many polymeric membranes such as copolymers based on polyoxyethylene glycols and polyethylene terephthalate act as homogeneous barriers (26). Transport is generally dependent on the relative adsorption of the molecules diffusing to the face of the membrane and solubility of these molecules in the membrane (26). The selectivity of polymeric membranes such as polystyrene (43) and ethyl cellulose (44) has been used for the enrichment of air with respect to oxygen and attempts to make these processes industrially feasible have been reported (45). The diffusion of gases in polymers follows the Arrhenius equation (46) and the temperature dependence of diffusion is given by

$$D = D_o\ e^{-\Delta Ea/RT} \qquad \text{(Eq. 3)}$$

where D_o is a constant, and ΔEa is the apparent activation energy for diffusion.

The methods to determine the diffusivity of water vapors through membranes have been considered in great detail (10). The uptake of moisture by hygroscopic substances could not be prevented by encapsulating them in gelatin capsules (47). The permeation of water vapors decreased with increased chain length of the acid moiety of cellulose ester membranes (48). The water vapor transmission initially decreased and then increased as the concentration of the plasticizers in polymer was gradually increased (49). The solubility of water and the Arrhenius parameters for the diffusion of water in a polymer differ above and below the temperature at which the slope of the volume-temperature curve for the polymer changes (50) — the "glass temperature" (51).

The extensive use of polymeric materials in the pharmaceutical industry for packaging purposes has initiated the investigation of polymer-drug interactions. Kapadia et al. (52) showed interaction between salicylic acid and Nylon 66 and calculated the heat of sorption from equilibrium sorption studies at several temperatures using the van't Hoff equation (53). The heat of sorption for this and in the subsequent work with other weak organic acids (54, 55) was low (1-4 Kcal./mole). The magnitude of the sorption decreased with decreases in the polarity of the solvent. The pH-sorption studies implied interaction of the unionized acids with the basic group in the polyamide. The diffusion within the polymeric material was shown to be the rate determining step with the heats of activation in the range of 10 - 20 Kcal./mole. Studies on the sorbic acid-Nylon interactions (56 - 60) confirmed the results obtained with weak organic acids.

One of the possible important uses of polymeric materials in the pharmaceutical industry is as coating material for sustained release products (61 - 64). Vinyl, acrylic and cellulosic polymers were shown to be good for prolonged action coatings based on their solubility in simulated gastric and intestinal fluids (62). Copolymer-coated prednisolone tablets extended absorption of prednisolone over a period of 10 - 12 hours in intact dogs and in segments of intestinal tracts (63). Silicone rubber which has been used extensively in the subcutaneous prosthetic devices (65) has been shown to be permeable to steroids (16), cardiac pacers (66) and some other materials (17, 18).

Lyman and coworkers (26, 67, 68) have prepared synthetic membranes with the express intent of endowing them with specific characteristics which would transfer substances by an adsorption and solubility mechanism and not by sieve action. When the weight percent of polyoxyethylene glycol, the hydrophilic monomer in the copolyether-ester membranes was increased, the rates of transfer of glucose and urea increased. The magnitude of the increase in rates was different for the two compounds and the authors postulated a different degree of association or partitioning with the membrane (30).

MATHEMATICS OF TRANSPORT PROCESSES

The mathematics of transport processes depends upon the model chosen for the particular transport phenomenon under consideration. This has been discussed in detail by Tuwiner (69), Jost (70), Crank (71) and Lakshminarayaniah (72). Higuchi and Higuchi (73) have given a theoretical analysis of diffusional movement through heterogeneous barriers.

A transport process is considered to be in the steady state when the amount of penetrant passing through a reference point in a membrane matrix is invariant with time. When the amount passing through a reference point varies with time, the process is said to be in the non-steady state.

When a membrane is interposed between a solution of the penetrant and a solvent, the penetrant is transported initially by a non-steady state process. This "lag period" continues until the amount leaving the membrane is equal to the amount entering. A steady state results when the concentrations of the solutions on either side of the membrane are kept constant. However, if the concentration of the solutions are allowed to equilibrate, the amount entering and leaving may be equal for all analytical purposes even though the rate of permeation will be changing with time as a function of the concentration gradient. This may be termed a "quasi-steady state" transport.

The rate determining factor in non-steady state transport through the membrane is the rate of diffusion in the membrane; in steady state transport it is the constant concentration gradient alone; and in quasi-steady transport both the concentration gradient and the rates of approach to equilibrium of both extra-membrane phases are rate determining. Fick's first law of diffusion (74) states that the rate of diffusion is proportional to the concentration gradient,

$$dA/dt = DSdC/dx \qquad \text{(Eq. 4)}$$

where A is the amount of penetrant in moles diffusing in time t in seconds through a membrane having a surface area of S $cm.^2$. The concentration gradient is dC/dx across the membrane in moles per liter-cm. and D is the diffusion coefficient in $cm.^2/sec$. The term x is the distance into the membrane in cm. The concentration of the penetrant at a particular position in a polymer at a given time is given by Fick's second law of diffusion

$$dC/dt = D\ S\ d^2C/dx^2 \qquad \text{(Eq. 5)}$$

where d^2C/dx^2 is the change in the concentration gradient as a function of the distance x within the membrane. The derivation of Fick's second law from Fick's first law is given in Appendix C-II.

For a steady state condition, the change in the concentration at any point in the membrane is zero.

$$dC/dt = 0 \qquad \text{(Eq. 6)}$$

Thus $$D\ S\ d^2C/dx^2 = 0 \qquad \text{(Eq. 7)}$$

and the concentration gradient is a constant

$$dC/dx = K \qquad \text{(Eq. 8)}$$

It follows from Eqs. 4 and 8 that

$$dA/dt = D\ S\ K = D\ S\ (C_2 - C_1)/X \qquad \text{(Eq. 9)}$$

where C_2 and C_1 are the invariant concentrations of the concentrated and dilute solutions in contact with the membrane surfaces respectively and X is the thickness of the membrane. This states that the rate of diffusion through a membrane of thickness X and surface area S is constant with time for a constant concentration gradient. Thus the total amount diffused can be plotted against time to obtain a straight line with slope of D S K from which the diffusion constant D can be calculated when S, C_2, C_1 and X are known.

A more rigorous mathematical treatment considers the concentrations of the penetrant at the membrane surfaces or in the first monolayer of the membrane material, instead of the concentrations in the solutions for the concentration gradient in Eq. 9. This equation may be written as

$$dA/dt = D' \; S \; (C_{m2} - C_{m1})/X \qquad \text{(Eq. 10)}$$

where C_{m2} and C_{m1} are the concentrations of penetrant at the two membrane surfaces and D' is the intrinsic diffusion constant. The concentrations are related to the activity of the penetrant in the membrane as

$$C_{m1} = a_{m1}/\gamma_m \quad \text{and} \quad C_{m2} = a_{m2}/\gamma_m \qquad \text{(Eq. 11)}$$

where a_{m1} and a_{m2} are the activities of the penetrant at the two surfaces and γ_m is the activity coefficient of the penetrant in the membrane material.

The relation between activities and concentration of penetrants in the solution is given by

$$a_{s1} = C_1\gamma_s \quad \text{and} \quad a_{s2} = C_2\gamma_s \qquad \text{(Eq. 12)}$$

where a_{s1} and a_{s2} are the activities of the penetrant in the solutions and γ_s is the activity coefficient of the penetrant in the solution. Assuming a rapid equilibration of penetrant between solutions and membrane material at the surfaces

$$a_{s1} = a_{m1} \quad \text{and} \quad a_{s2} = a_{m2} \qquad \text{(Eq. 13)}$$

From Eqs. 11, 12, and 13 it follows that

$$C_{m1} = C_1 \gamma_s/\gamma_m \quad \text{and} \quad C_{m2} = C_2 \gamma_s/\gamma_m \qquad \text{(Eq. 14)}$$

When these values of C_{m1} and C_{m2} are substituted in Eq. 10, the following expression is obtained

$$dA/dt = (D' \, S \, \gamma_s/X \, \gamma_m)\,(C_2 - C_1) \qquad \text{(Eq. 15)}$$

Since the ratio of activity coefficients is the partition coefficient Kp

$$\gamma_s / \gamma_m = Kp \qquad \text{(Eq. 16)}$$

Eq. 15 may be rewritten as

$$dA/dt = (D' \, SK_p/X)\,(C_2 - C_1) \qquad \text{(Eq. 17)}$$

The product $D'K_p$ is the term D in the original Fick's diffusion equation (74) and is termed the permeability constant for the system.

The time lag method used extensively (46, 75, 76) for the calculation of diffusion constant in the non-steady state is based on the premise that a finite amount of time will be needed for a penetrant to traverse the thickness of the membrane before the attainment of a steady state (76). After this initial lag period, when the concentrations on both sides of the membrane are constant, the plot of the amount diffused versus time will be a straight line (Eq. 17) which when extrapolated will give an intercept θ on the time axis.

$$\theta = X^2 / 6 D' \qquad \text{(Eq. 18)}$$

The mathematical basis for this method is

$$A = D S C_2 (t - X^2 / 6 D) / X \qquad \text{(Eq. 19)}$$

derived partially in Appendix C-III. This equation may be written in terms of the partition coefficient Kp and the intrinsic diffusion coefficient D' as (73)

$$A = (D' S Kp C_2 / X) (t - X^2 / 6 D') \qquad \text{(Eq. 20)}$$

Thus the slope of the plot of the amount diffused versus time, for a constant concentration gradient in the membrane, will be $D' S Kp C_2/X$. The Eq. 20 is the more rigorous version of Eq. 17 with $C_1 = 0$.

In the equilibrium diffusion experiments, the concentration gradient across the membrane decreases to zero (77). The mathematical expression derived for this quasi-steady state is given in Appendix C-IV and is (78)

$$[XV_1V_2/S(V_1 + V_2)] \ln (C_2 - C_1)/C_o) = -Dt \qquad \text{(Eq. 21)}$$

where V_1 and V_2 are the volumes of the solutions in the compartments with molar concentrations C_1 and C_2. C_o is the concentration in one compartment at $t = 0$. When the volumes V in the two compartments are equal Eq. 21 simplifies to

$$(XV/0.869\ S)\ \log\ (C_2 - C_1/C_o) = -Dt \qquad \text{(Eq. 22)}$$

An alternate method is the method of Berthier (79) wherein the fractional uptake has been used for the calculation of diffusion constants (52). This method has been explained in Appendix C-V.

EXPERIMENTAL

Materials

Polymer Films:

RILSAN (Nylon 11) - (May Industries Inc., Atlanta, Ga.) is 11-amino undecanoic acid polymer (80).

POLYPENCO (Nylon 101) - (The Polymer Corporation, POLYPENCO Division, Reading, Pa.) is a polyamide (81).

Cellulose Acetate (KODACEL A 29), Cellulose Triacetate (KODACEL TA 401), and Cellulose Acetate Butyrate Sheets (KODACEL B 298) (Eastman Chemical Products, Inc., Kingsport, Tennessee) are thermoplastic cellulosic films (82).

Polyethylene Type B, Mylar Polyester Type S (E.I. DuPont De Nemours and Co., Inc., Wilmington, Delware). Mylar Polyester is polyethylene terephthalate (83, 84).

Polypropylene (Avisun Corporation, 215, 12th Street, Philadelphia, Pa.) (85).

Silastic Medical Grade Sheeting (H-0169, H-0293) (Dow Corning Center for Aid to Medical Research, Midland, Michigan) is a dimethylsiloxane polymer (86).

Chemicals:

The following chemicals were supplied by Abbott Laboratories, North Chicago, Illinois.

Amobarbital - Equivalent weight.—Calculated for $C_{11}H_{18}N_2O_3$: 226.28. Found: 236.64.

Barbital - Equivalent weight.—Calculated for $C_8H_{12}N_2O_3$: 184.20. Found: 197.03.

Butabarbital - Equivalent weight.—Calculated for $C_{10}H_{16}N_2O_3$: 212.23. Found: 215.15.

Cyclobarbital - Equivalent weight.—Calculated for $C_{12}H_{16}N_2O_3$: 236.26. Found: 245.20.

Diallylbarbituric Acid - Equivalent weight.—Calculated for $C_{10}H_{12}N_2O_3$: 208.21. Found: 201.72.

Mephobarbital - Equivalent weight.—Calculated for $C_{13}H_{14}N_2O_3$: 246.26. Found: 250.0.

Metharbital - Equivalent weight.—Calculated for $C_9H_{14}N_2O_3$: 198.23. Found: 200.92.

Pentobarbital - Equivalent weight.—Calculated for $C_{11}H_{18}N_2O_3$: 226.26. Found: 231.5.

Phenobarbital - Equivalent weight.—Calculated for $C_{12}H_{12}N_2O_3$: 232.24. Found: 256.76.

Secobarbital - Equivalent weight.—Calculated for $C_{12}H_{18}N_2O_3$: 238.29. Found: 229.55.

Thiamylal - Equivalent weight.—Calculated for $C_{12}H_{17}N_2O_2S$: 254.34. Found: 289.80.

Thiopental sodium - Equivalent weight.—Calculated for $C_{11}H_{18}N_2O_2S$: 242.33. Found: 246.30.

The following chemicals were supplied by Smith Kline and French Laboratories, Philadelphia, Pa.

α-methylphenethylamine hydrochloride - Equivalent weight.—Calculated for $C_9H_{13}N.HCl$: 171.5. Found: 165.3.

α-ethylphenethylamine hydrochloride - Equivalent weight.—Calculated for $C_{10}H_{15}N \cdot HCl$: 185.5. Found: 203.1.

2-amino-4-methyl-4-phenylpentane hydrochloride - Equivalent weight.—Calculated for $C_{12}H_{19}N \cdot HCl$: 213.5. Found: 205.31.

3-amino-1-phenylbutane sulfate - Equivalent weight.—Calculated for $(C_{10}H_{15}N) \cdot H_2SO_4$: 198. Found: 242.13.

1-methyl-5-phenylpentylamine hydrochloride - Equivalent weight.—Calculated for $C_{12}H_{19}N \cdot HCl$: 213.5. Found: 355.93.

The following compounds were purchased from Eastman Organic Chemicals, Rochester, 3, New York.

4'-Aminopropiophenone - Melting point 139 - 140.5°; literature value 140° (87).

4'-Aminoacetophenone - Melting point 105 - 106°; literature value 106° (87).

3'-Aminoacetophenone - Melting point 97 - 99°; literature value 99° (87).

The following compounds were supplied by The Upjohn Company, Kalamazoo, Michigan.

Progesterone - Melting point 128 - 130°; literature value 127 - 131° (87).

Cortisone - Melting point 230 - 236°; literature value 236 - 240° (87).

Hydrocortisone - Melting point 217 - 220°; literature value 217 - 220° (87).

Prednisolone - Melting point 239 - 240°; literature value 240 - 241° (87).

The following compounds were purchased from National Biochemical Corporation, Cleveland, Ohio.

Sulfathiazole - Melting point 200 - 203°; literature value 200 - 204° (87).

Sulfisoxazole - Melting point 195 - 198°; literature value 194° (87).

Sulfabenzamide - Melting point 181 - 183°; literature value 181.2 - 183.3° (87).

Sulfadiazine - Melting point 256 - 257°; literature value 252 - 256° (87).

Tetraethylthiuram disulfide - (Disulfiram) (Ayerst Laboratories, Incorporated, New York, N. Y.) Melting point 70 - 72°; literature value 70° (87).

Dextromethorphan - (Vick Divisions Research and Development, Richardon-Merrell Inc., Mt. Vernon, New York).

Peanut oil and Mineral oil used were of United States Pharmacopoecial grade.

Methods of Analysis

All compounds used in this investigation except ethanol were analyzed spectrophotometrically by the Cary Model 15 dual beam recording spectrophotometer, Beckman Model DU spectrophotometer or Beckman Model DU-2 spectrophotometer. Standard, square, silica cells of 10 mm. light path (Sargent # S-75730) were used. All spectrophotometric measurements were made at 24.0 ± 1.0°.

Spectrophotometric measurement of absorbances was used for the quantitative estimation of barbituric acid derivatives, aminoalkylphenones, progesterone, phenylalkylamines and dextromethorphan. The linear relationship between the absorbance of drug solutions and their concentrations in accordance with Lambert-Beer's law (88) was verified in all cases. A few representative calibration curves are shown in Fig. 1.

The absorbances of solutions of barbituric acid derivatives were measured in pH 10.1 borate buffer as the molar absorptivities (ϵ values) of their anionic forms are much higher than those in the uncharged form. Absorbances of all barbituric acid derivatives except thiamylal and thiopental were measured at a wavelength of 238 mμ. The wavelength of 238 mμ is not the λ_{max} of all these compounds. However, measurements at one wavelength were found to be convenient and time saving. The absorbances of thiamylal and thiopental were measured at their λ_{max} of 304 mμ. The wavelengths of absorbance measurement and the ϵ values at these wavelengths are recorded in Table I.

The absorbances of dextromethorphan, progesterone and aminoalkylphenones were measured in pH 6.8 phosphate buffer solutions. The wavelengths at which the absorbances were measured and the ϵ values at these wavelengths are shown in Table I.

The phenylaklylamines-α-methylphenethylamine, α-ethylphenethylamine, 1-methyl-5-phenylpentylamine, 3-amino-1-phenyl-butane and 2-amino-4-methyl-4-phenylpentane were analyzed colorimetrically by the method of Gettler and Sunshine (89) modified in the following manner: A 1.00 ml. sample of phenylalkylamine (1.5×10^{-5} - 1.0×10^{-4} M) in pH 6.8 phosphate buffer was transferred to a 6" x 5/8" pyrex test tube. The solution was made alkaline with 0.1 ml. solution of 2 N NaOH and was mixed on a Vortex Jr. Mixer. Five ml. of chloroform (A. R. Grade) was then added and mixed on the Vortex Jr. Mixer for about 1 minute. The solution was centrifuged at about 3,200 r.p.m. for 3 minutes. A 4 ml. pipette was inserted through the aqueous layer into the chloroform layer blowing lightly through the pipette to avoid entry of the aqueous solution. Four ml. of the chloroform was removed and transferred into a test tube of similar dimensions. Two-tenth ml. of freshly prepared methyl orange reagent (equal volumes of saturated solutions of methyl orange and boric acid in water) was added and mixed for about one minute. This solution was centrifuged at 3200 r.p.m. for 3 minutes and 3 ml. of the chloroform layer was carefully pipetted into another test tube. Then 0.2 ml. of absolute ethanol containing 2% concentrated sulfuric acid was added. The solution was mixed and then transferred to a cuvette for the measurement of absorbance against the chloroform layer obtained from a phosphate buffer blank treated identically. The absorbance was measured on a Beckman DU spectrophotometer at 520 mμ. A five point calibration curve was prepared each day the samples from the diffusion were analyzed.

The remaining compounds - cortisone, hydrocortisone, prednisolone, sulfadiazine, sulfathiazole, sulfisoxazole, sulfabenzamide and disulfiram - were used only in the screening part of this investigation. Spectrophotometric methods were used only for their qualitative analysis and no attempt was made to verify the absorbance - concentration linearity.

Since the λ_{max} and ϵ values of all steroids were independent of the pH of the solution, the spectra of their solutions were obtained without any adjustment of pH.

The solutions of sulfadiazine, sulfathiazole, sulfisoxazole and sulfabenzamide were made alkaline with NaOH solution before obtaining their U.V. spectra on the Cary spectrophotometer. The λ_{max} and the ϵ values of these compounds are given in Table 1.

Disulfiram was qualitatively analyzed by a method involving chelation with copper ion (90). Five ml. of 0.02 $\underline{M}$ $CuSO_4$ solution in pH 6.5 phosphate buffer was added to 10 ml. of solution of disulfiram in phosphate buffer. The solution was mixed on Vortex Jr. Mixer. The copper complex formed was extracted into 5 ml. of ethylene dichloride with vigorous mixing on the Vortex Jr. Mixer for 1 minute. The ethylene dichloride layer was separated and its absorbance was measured against the ethylene dichloride layer obtained from identical treatment of a phosphate buffer blank. The disulfiram-copper complex showed two peaks at wavelengths of 272 and 285 mμ.

Ethanol was quantitatively determined using vapor phase chromatography. An F & M Model 700 Gas Chromatograph with flame ionization detector was used with a 4' × 1/4" o.d. stainless steel column packed with 20% Carbowax 20 M. on 60-80 mesh Chromosorb W, worked isothermally at 50.0°. The temperature of the detector was 250.0°, and that of injection port was 150.0°. The carrier gas, helium, was used at a pressure of 30 psig. while hydrogen and air for the flame were used at 10 and 40 psig. respectively. Samples of five microliters of aqueous ethanol were injected without any prior treatment. The peak heights were measured and the concentration of the ethanol in the sample was obtained from a calibration curve prepared with ethanol solutions of known concentrations.

Determination of pKa.—The pKa is the negative logarithm of the acid dissociation constant. The pKa's of barbituric acid derivatives, dextromethorphan and phenylalkylamines were determined by potentiometric titration. The pKa of 4'-aminopropiophenone was determined spectrophotometrically.

The potentiometric titrations were performed with a Sargent Model D automatic titrator. The titrator was equipped with a syringe with a titrant capacity of 2.5 ml. The pH scale of the titrator was standardized with two of the pH 4.0, 7.0 and 10.0 standard Beckman buffer solutions (Beckman Instrument, Inc., Fullerton, California) bounding the pH range to be titrated. The accuracy of the pH measurement was ± 0.05 pH unit. All titrations were performed at 24.0 ± 1.0°.

The barbituric acid derivatives were dissolved in 2 ml. of 0.04 N NaOH and the solution was diluted with freshly boiled distilled water. A 20 ml. aliquot of this solution was titrated with 0.1 N $HClO_4$ on the titrator.

The acid salts of phenylalkylamines were dissolved in distilled water to contain about 5 milliequivalent of accurately weighed compound in 30 ml. of distilled water. The solutions were titrated on the titrator against 0.1 N NaOH.

A weighed quantity of dextromethorphan was dissolved in 2 ml. of 0.01 N HCl and the solution was diluted to 40 ml. This solution was titrated against 0.1 N NaOH. In all these titrations an equal volume of the blank solution was titrated under identical conditions. The calculated equivalent weights are given in the section on materials.

The pKa of a compound was determined from these titration curves by the method of Parke and Davis (91) wherein the difference between the volumes of the titrant for attaining the same pH for the sample and blank solutions was plotted against the pH. The pH value corresponding to the midpoint of the resultant sigmoidal curve was the half neutralization point or the pKa of the compound.

The pKa of 4'-aminopropiophenone was determined spectrophotometrically. Hundred ml. of 8.56 X 10^{-5} M solution was used. The pH of the solution was measured on the Beckman Expanded Scale pH meter standardized with pH 4.0 and 7.0 standard Beckman buffer solutions. An ultraviolet spectrum of this solution was obtained against a distilled water blank on the Cary Recording spectrophotometer. The sample solution in the cuvette was returned to the bulk solution. A drop of concentrated HCl was added and the solution was stirred on a magnetic stirrer. The pH of the solution was measured and a U.V. spectrum was obtained again. Thus, U.V. spectra of the solutions were obtained for several pH values. The absorbance of the solutions at a wavelength of 307 mμ was measured from recorded spectra and plotted against the pH of the solutions. The pH value corresponding to the midpoint of the resultant sigmoidal curve was the half-neutralization point or pKa of 4'-aminopropiophenone. The pKa values of the compounds are reported in Table I.

Determination of ϵ values.—A weighed amount of barbituric acid derivative was dissolved in 2 ml. of 0.04 N NaOH solution and diluted to a total volume of 25 ml. with freshly boiled distilled water. Twenty ml. of the solution was pipetted into a 30 ml. beaker and titrated against 0.10509 N $HClO_4$ on the Sargent Model D automatic titrator. The molarity of the compound present in the 20 ml. solution was calculated from the volume and normality of $HClO_4$ used in the titration. The remaining 5 ml. of the solution was diluted with pH 10.1 borate buffer solution to obtain 5 different concentrations of the solution whose absorbances were then measured on the Beckman DU spectrophotometer at wavelength of 238 mμ for all the barbituric acid derivatives except thiamylal and thiopental whose absorbances were measured at 304 mμ. The absorbances so obtained were then plotted against the molarity of the solution and ϵ values were calculated from the slope by the equation (88)

$$\epsilon = \text{Absorbance} / \text{Concentration} \qquad \text{(Eq. 23)}$$

The compounds 4'-aminopropiophenone, 4'-aminoacetophenone, 3'-aminoacetophenone, progesterone, dextromethorphan were weighed accurately into a volumetric flask. These were dissolved in distilled water and the absorbances of the adequately diluted solutions were measured. The ϵ values were then calculated by Eq. 23. The ϵ values are reported in Table I.

Screening of Polymer Films for the Permeability To Drugs

The polymer films Rilsan, Polypenco, cellulose acetate, cellulose triacetate, cellulose acetate butyrate, polyethylene, Mylar polyester, polypropylene and Silastic were used in thicknesses of 5, 5, 5, 3, 3, 3, 3, 5, and 3 mil respectively.

The membranes were washed in running tap water and then with distilled water. These membranes were then dried and cut into small pieces ($\frac{1}{2}$" x $\frac{1}{2}$").

Saturated solutions of 4'-aminopropiophenone, 4'-aminoacetophenone, 3'-aminoacetophenone, sulfadiazine, sulfathiazole, sulfabenzamide, sulfisoxazole, disulfiram, barbital, phenobarbital, progesterone, cortisone, prednisolone in 0.1 N HCl, 0.1 N NaOH, pH 6.8 phosphate buffer, propylene glycol, peanut oil, ethanol, mineral oil, ethylene glycol and polyethylene glycol 200 were used.

Glass serum vials of 10 ml. capacity with rubber stoppers and aluminum caps were thoroughly cleaned and dried. A hole was bored into the rubber stopper with a # 3 cork-borer. About 2 ml. of a saturated solution of a drug under study was delivered into the serum vial without touching its lip. The vial was stoppered with a rubber stopper with a hole in it. A small piece of the membrane under study was laid flat on the stopper to cover it completely and an aluminum cap was then crimped on the rubber stopper so as to sandwich the membrane between the two. The sketch of an assembled vial is shown in Fig. 2. The detachable circular disc in the aluminum cap was removed to expose the membrane. The serum vial was then inverted and placed into a two oz. ointment jar containing about 10 ml. of pH 6.8

phosphate buffer. The jars were capped, properly labelled and set aside for at least one week.

After this time the phosphate buffer solution in each jar was qualitatively analyzed on a Cary Model 15 recording spectrophotometer. In the cases of the barbituric acid derivatives and sulfonamides, the phosphate buffer solutions from the jar were made alkaline before reading them on the spectrophotometer. Disulfiram was chelated with copper and the chelate was extracted into ethylene dichloride. The spectrum of the ethylene dichloride solution was then obtained on the spectrophotometer.

A drug was said to have permeated through a membrane when the peaks at wavelengths corresponding to the $\lambda_{max.}$ values of the drug were observed in the spectrum. Experiments with positive results were repeated to avoid the acceptance of leaking vials as evidence for permeation. Solvents without drugs were put in the vials to test their permeability through the membranes and their effect on the rubber stopper and the membranes.

Diffusion Apparatus

The diffusion apparatus consisted of diffusion cells, beakers, Durrum 12-Channel Dial-A-Pump, and a stirring device.

Diffusion cells.—Two types of diffusion cells were designed to study the steady state and quasi-steady state diffusion.

The steady state diffusion cell designed was a modification of the cell used by Lyman *et al.* (68). An exploded schematic view of the diffusion cell is shown in Fig. 3. It consisted of two stainless steel plates (2 1/2" x 2" x 1/8"), a glass T joint, two silicone rubber gaskets (2.57 cm. i.d. × 2.95 cm. o.d. × 0.16 cm. thick) and a set of four stainless steel nuts and bolts.

Each of the stainless steel plates had a hole in the center, 2.57 cm. in diameter. Around this hole there was a border 0.43 cm. in width from the perimeter of the hole and recessed 2 mm. into one face of the stainless steel plate. The silicone gaskets fit into the recessed borders around the holes. The two plates had four holes in four corners for the stainless steel bolts.

The glass T joint consisted of a 3 cm. long hollow glass cylinder 2.60 cm. in diameter joined in its center at right angles on one side to an 11 cm. long glass tube 0.8 cm. in diameter to form a hollow T shaped device. The two annular edges of the glass cylinder fitted into the recessed borders against the gaskets in the plates.

A piece of membrane under study was positioned between the recessed border of each of the plates and a silicone rubber gasket. The open ends of the glass cylinder were then fitted into the recessed borders on the face of the silicone rubber gaskets. The whole assembly was held in position by a set of four nuts and bolts passing through the holes in the corners of the plates. The volume of the assembled cell was approximately 22 ml. and the total area of the two membranes available for diffusion was 10.4 cm.^{2}.

The quasi-steady state diffusion cell (see Fig. 4) consisted of two stainless steel plates (2 1/2" × 2 1/2" × 1/8"). Each of these plates was welded to one end of a stainless steel tube (1 1/2" in diameter and 7" long) at an angle of 45°. Each plate had a hole in the center (3.1 cm. in diameter) with a circular border 0.8 cm. in width from the perimeter of the hole and recessed 2 mm. into the face of the plate. The plates had four holes in the four corners for the stainless steel bolts. Two silicone rubber gaskets (3.1 cm. i.d. × 3.8 cm. o.d. × 3 mm. thick) fitted into the recessed border around the holes in the plates. A membrane under study was clamped between the two silicone rubber gaskets placed in the recessed borders in the plates. The plates were then clamped together with four stainless steel nuts and bolts. The diffusion cell when assembled formed a V shaped device and held 150 ml. of solution in each of the tubes. The area of the membrane available for the diffusion was 7.55 cm.^{2}

Beakers.—A 200 ml. or 400 ml. Pyrex beaker was used with each steady state diffusion cell. A plastic cover was fabricated for each beaker from a disposable polyethylene Petri dish. The rim of the Petri dish was sawed off at one position to accommodate the beak of the beaker. A hole, 1/2" in diameter, was burned into the center of the cover with a hot glass rod. Another hole of the same size was made in the cover about 1" away from the center.

Durrum 12-Channel Dial-A-Pump.—This pump (Durrum Instrument Corporation, 925, E. Meadow Drive, Palo Alto, California) was used for pumping a solution from a reservoir into the diffusion cell and back. The pumped fluids entered the pumping unit by way of plug-in flexible plastic tubing, received their pumping action by a flat pressure plate vertically cycling against a series of independently, adjustable backing blocks, and emerged by way of another plug-in connection similar to input. The resilient pumping tubes used were amber latex surgical tubing (Rubber Latex Products, Inc., Cuyaholga Falls, Ohio) 5/16" o.d. × 3/16" i.d. Each channel used two pieces of vinyl tubing (Becton, Dickinson and Company, Rutherford, N. J.) 3/16" o.d. × 1/16" i.d.

One piece of the tubing carried the solution from a container through the plug-in connection into the pumping tube. The exit was connected via a plug-in connection to another piece of tubing that delivered the solution from the pumping tube to its destination.

Stirring device.—A thermostated shaker bath (American Instrument Company, Silver Spring, Maryland and Eberbach Corporation, Ann Arbor, Michigan) shook the beakers and agitated the solutions in the beakers besides keeping the temperature of the solutions in the diffusion cell assembly constant within ± 0.5°. The shaking rate of the bath was 108 strokes per minute with each stroke traveling a distance of 1 1/2".

Two other stirring devices tried were Mag-Jet stirrers (Will Scientific, Atlanta, Georgia, Catalog # 25212) and nitrogen bubbling. The Mag-Jet stirrer kept underneath a beaker was operated by water pressure and rotated a magnetic stirring rod in the beaker and another magnetic stirring rod in the diffusion cell kept in the beaker. The speed of the Mag-Jet stirrer decreased slowly to zero in 5 to 6 hours probably due to deposition of salts in the small clearance between the rotor and its metal casing.

Nitrogen under pressure was bubbled through the solutions in the diffusion cell and the beaker, using narrow bore glass tubing. It was observed that the solutions were stirred only at the spot of the bubbling. The bubbling of the gas was, therefore, not useful for stirring a large volume of the solution in the beaker. Also the bubbling of the gas over a long period of time through the solution caused evaporation of the solution. The volume of the solution in the beaker was always critical because the amount of drug diffusing through the membrane was calculated from the concentration and the volume of the beaker solution. When the solution used in the diffusion cell was a saturated solution, the bubbling of the gas was used as a stirring device. The volume of the solution in the diffusion cell was not critical and the evaporation of the saturated solution did not in any way affect the concentration of the drug in the solution. The small volume of the saturated solution in the cell could therefore be well agitated by nitrogen gas bubbling method.

The Durrum 12-Channel Dial-A-Pump pumped the solution of a drug in and out of the steady state diffusion cell and was observed to be a good method of agitating the solution in the diffusion cell (see Fig. 5). The drug solution from a reservoir was pumped into the cell through one channel at the rate of 25-30 ml. per minute. The end of the delivery tube from this channel reached the diametric center of the horizontal portion of the glass T joint of the assembled diffusion cell. Another tube carried the solution from the cell to the channel which pumped the solution at the rate of 35-40 ml. per minute. The end of the tube carrying the solution from the cell to the pumping tube, was adjusted in the stem of the cell at the level of the solution in the beaker. Since the channel carrying the solution out of the cell pumped the solution at a rate faster than the other channel pumping the solution into the cell, the level of the solution in the cell was maintained at the level of the solution in the beaker. The pulsating action of the pump kept the solution in the cell well agitated besides renewing its contents every few minutes because of the high turnover of the solution. The thermostated shaker bath held the diffusion assembly rigidly in a metal rack fixed to the shaker tray and agitated the solution in the beaker maintaining the temperature of the solutions constant.

The solutions in the arms of the quasi-steady state diffusion cell were agitated by the thermostated shaker bath in which the cell was wired to the shaker tray.

Solubility Studies

Saturated solutions of barbituric acid derivatives in pH 4.7 acetate buffer (μ = 0.1) were prepared at 50.0°. These solutions were then allowed to cool to 25.0° in the thermostated shaker bath and to equilibrate at that temperature for 48 hours in presence of excess solids. Similarly saturated solutions of aminoalkylphenones were prepared in pH 6.8 phosphate buffer (μ = 0.3) at 50.0° and equilibrated to 37.5° in the thermostated shaker bath. The saturated solutions of 4'-aminopropiophenone in pH 6.8 phosphate buffer containing 0, 10, 20, 30 and 40% ethanol were prepared by vigorously shaking the solutions at room temperature in presence of excess solids and allowed to equilibrate at 25.0° in the thermostated shaker bath for 48 hours.

The solutions were filtered by suction through electrode isolation tubes (E. H. Sargent & Co., 4647 West Foster Avenue, Chicago, Illinois, Catalog # S-30417). The electrode isolation tube is a tube fitted with a finely porous fritted glass membrane and is 125 mm. long and 13 mm. in diameter in its lower section, 10 mm. in diameter in upper section. Aliquots of the filtered solutions of barbituric acid derivatives were appropriately diluted with pH 10.1 borate buffer. Aliquots of filtered solutions of aminoalkylphenones were appropriately diluted with pH 6.8 phosphate buffer. The absorbances of these diluted solutions were measured on a spectrophotometer at the pertinent wavelengths reported in Table I. The solubilities of these compounds in respective buffer solutions were then calculated from these absorbance values and the knowledge of their ϵ values reported in Table I.

The solubility values of 4'-aminopropiophenone in phosphate buffer containing 0, 10, 20, 30 and 40% ethanol were plotted against the concentration of ethanol in the phosphate buffer solutions as shown in Fig. 6. This curve was used as a calibration curve to obtain the solubility of 4'-aminopropiophenone in phosphate buffer containing 7.5, 15, 22.5, 30 and 37.5% ethanol.

Determination of Partition Coefficients

The coefficients of partition between the solutions of barbituric acid derivatives in acetate buffer, aminoalkylphenones in phosphate buffer, and an organic liquid were determined at room temperature. The organic liquids used were chloroform, mineral oil, cyclohexane and silicone liquid 200.

The aqueous media used for the preparation of the solutions of these compounds and the organic liquids used for the partitioning were saturated with respect to each other by shaking them together in large quantity and then separating them, first by separatory funnel and then by centrifugation at 3200 r.p.m. for five minutes.

An approximate 5×10^{-4} $\underline{M}$ solution of a barbituric acid derivative was prepared in pH 4.7 acetate buffer presaturated with chloroform. One ml. of this solution was diluted with 10 ml. of pH 10.1 borate buffer and its absorbance was measured on Beckman DU spectrophotometer at wavelength reported in Table I. The blank solution for the absorbance measurement consisted of acetate buffer medium presaturated with chloroform and diluted 10 times with pH 10.1 borate buffer. The pH of the diluted solution was observed to be 10.1. Generally the concentration of the compound in the solution used was such that the diluted solution would have an absorbance between 0.5 and 0.7. Five ml. of the solution in acetate buffer was transferred to a 10 ml. glass vial. Five ml. of chloroform presaturated with acetate buffer was added to it. The vial was closed with a rubber stopper and sealed with an aluminum cap. The solution was mixed on a Vortex Jr. Mixer for 3 minutes. The solution was then centrifuged at 3200 r.p.m. for about 3 minutes. About 3 ml. of the aqueous layer was withdrawn from the vial with a glass syringe and a needle and transferred to a test tube. One ml. of this solution was then diluted with 10 ml. of pH 10.1 borate buffer and its absorbance was measured against an acetate buffer blank treated identically. The difference between the absorbances of the aqueous solution before and after the partitioning represented the concentration of the substance partitioned into the chloroform layer. The ratio of the difference in absorbances to the absorbance of the aqueous layer after partitioning was the partition coefficient for the barbituric acid derivative between its solution in acetate buffer and chloroform.

The same procedure was used for studying the partitioning of barbituric acid derivatives between their solutions in acetate buffer and the organic phases, cyclohexane and silicone liquid 200. The amounts partitioned into these organic phases were very small and gave small differences between the absorbances of the acetate buffer layer before and after the partitioning with these organic liquids. A small error in the absorbance measurement therefore introduced large error in the calculation of the partition coefficient. Hence these values were not used in further investigation and have not been reported.

The coefficients of partition of aminoalkylphenones - 4'-aminopropiophenone, 4'-aminoacetophenone, and 3'-aminoacetophenone - between their solutions in pH 6.8 phosphate buffer and chloroform were determined by the method described for barbituric acid derivatives.

Measurement of Thickness of Membranes

The silastic membranes were available in four different labelled thicknesses of 3, 5, 10 and 20 mil. The actual thickness of each membrane was measured with a micrometer screw capable of measuring a minimum thickness of 0.1 mil. A clean sheet of paper was cut into a rectangle measuring 2 1/2" x 5". This was folded into a square of 2 1/2" x 2 1/2". The paper was marked lightly with a pencil in a square pattern of 1" x 1" from number 1 to 9. The thickness of the paper at each number was measured with the micrometer screw. A membrane was carefully placed flat between the folded paper and the thickness was measured at each number again. The thickness of the membrane was then obtained by difference. The measurements were made on seven different pieces of the similarly labelled thicknesses of the membrane.

Study of Permeability of Silastic Membrane to Phosphate Buffer Salts and Hydrochloric Acid

A steady state diffusion cell was assembled with 5 mil. thick silastic membrane in position. It was filled with about 20 ml. of distilled water. The cell was kept in a 400 ml. beaker containing about 250 ml. of pH 6.5 phosphate buffer ($\mu = 1.2$). A sample of distilled water from the cell was tested after 15 hours for the presence of PO_4^{3-} by the ammonium molybdate test (92).

Another diffusion cell filled with 20 ml. distilled water was kept in a beaker containing 250 ml. of 0.1 N HCl solution. The distilled water inside the cell was tested for the presence of chloride ions after 11 hours by the silver nitrate test (93). The pH of the distilled water was also measured.

Two-tenths of a ml. of 0.6 M and 5 ml. of 4.80×10^{-4} M phosphate buffer solutions were diluted to 250 ml. with distilled water to obtain 4.80×10^{-4} M and 9.60×10^{-6} M phosphate buffer solutions respectively. Ammonium molybdate reagent (92) was prepared by dissolving 1.59 g. of molybdic acid in 3.5 ml. of concentrated ammonia solution diluted with 3.5 ml. of water. This solution was slowly added to a mixture of 8 ml. of concentrated nitric acid and 10 ml. of distilled water. Three ml. of this ammonium molybdate reagent was added to 3 ml. of sample solution for testing the presence of phosphate salts.

The silver nitrate solution used for testing the presence of chloride ions was prepared by dissolving 2 g. of silver nitrate in 20 ml. of distilled water. The sample to be tested for the presence of chloride ions was acidified with a drop of concentrated nitric acid and an equal volume of 10% silver nitrate solution was added. A solution of 4×10^{-5} N HCl was used as a standard solution for the test.

Preparation of Solutions

The solutions of aminoalkylphenones were prepared in pH 6.8 phosphate buffer. A weighed amount of a compound (about 2.5 g.) was dissolved in a known volume (about 100 ml.) of 0.4 N HCl. A known aliquot of this solution (usually 20 ml.) was then diluted with pH 6.8 phosphate buffer (μ = 0.3) to 2 liters.

Aliquots of 4'-aminopropiophenone solution in 0.4 N HCl were diluted to 2 liters with acetate buffers and phosphate buffer of different pH values and hydrochloric acid solutions of different normalities. These solutions were then used to study the effect of pH on the diffusion of 4'-aminopropiophenone through Silastic membrane.

The solutions of barbituric acid derivatives - amobarbital, barbital, cyclobarbital, diallylbarbituric acid, mephobarbital, metharbital, pentobarbital, phenobarbital, secobarbital, thiamylal and thiopental - were prepared in pH 4.7 acetate buffer. A known amount (about 0.5 g. in the case of mephobarbital, thiamylal and thiopental and 1.0 g. in the case of the remainder of the barbituric acid derivatives) was dissolved in 20 ml. of 0.1 N NaOH and then diluted with pH 4.7 acetate buffer (μ = 0.1) to 2 liters. Similarly 2 liters of the solutions of barbital and pentobarbital were also prepared in acetate, phosphate and borate buffers of different pH values to study the effect of pH on the rate of diffusion of these barbituric acid derivatives.

Solutions of α-methylphenethylamine hydrochloride, 2-amino-4-phenylpentane hydrochloride, 3-amino-1-phenylbutane sulfate, 1-methyl-5-phenylpentylamine hydrochloride and α-ethylphenethylamine hydrochloride were prepared in borate buffer. A known amount (about 0.5 g.) of a drug was dissolved in 20 ml. of distilled water and diluted with 0.1 N NaOH to 2 liters. The pH of the solution was then adjusted with boric acid solution to a value close to the pKa value of the drug. (The pKa values of these compounds are given in Table I). The pH values of the final solutions of the compounds in the order listed above were 8.93, 9.45, 9.40, 9.60 and 9.28 respectively.

A saturated solution of dextromethorphan was prepared in pH 10.1 borate buffer by equilibrating the solution at the temperature of study in presence of excess of undissolved dextromethorphan for about 12 hours. The saturated solution of progesterone was prepared in the same way in pH 6.8 phosphate buffer solution.

A Typical Steady State Diffusion Experiment

A strip of Silastic membrane was washed with water several times to remove the sodium bicarbonate dusting powder from its surfaces. The membrane was finally washed with distilled water and dried in air. It was then cut into 2" x 2" pieces. A steady state diffusion cell was assembled and two such pieces of Silastic membrane were fixed in position between the stainless steel plates and silicone gaskets. (See Fig. 5.)

The diffusion cell was filled with the buffer solution used for the preparation of the solution of the drug under study. The level of this solution in the stem of the glass T was kept about 1 1/2" above the horizontal portion of the T joint. The cell was then placed in a 200 or 400 ml. capacity beaker. The beaker contained either 120 or 200 ml. of 0.1 N HCl, borate buffer or phosphate buffer solution. The solvents chosen depended on the drug under study. The beaker was then covered with a piece of Parafilm (American Can Company, Neenah, Wisconsin) with a hole in it for the stem of the diffusion cell. The Parafilm was then taped to the sides of the beaker. The beaker was covered with a plastic Petri dish with two holes in it. The stem of the diffusion cell was inserted through one hole and the other hole was used to remove the samples from the solution in the beaker. The Petri dish cover was taped to the sides of the beaker. The Petri dish cover held the diffusion cell immobile in the beaker and prevented the widening of the hole in the Parafilm by the stem of the diffusion cell, and thus minimized the evaporation or contamination of the solution in the beaker.

The beaker with the diffusion cell was fitted rigidly in the metal rack resting in the shaker bath. This assembly was allowed to equilibrate at the temperature of the bath for about 10 hours. A two liter solution of the drug under study was also allowed to equilibrate in another constant temperature bath maintained at the same temperature. This solution was used as reservoir of the drug solution for the diffusion experiment.

The pump was started with the ends of all four vinyl tubing from the two channels dipping in the drug solution. The pumping was continued until the tubes were full with the drug solution. After thermal equilibration a hole was burned into the Parafilm by passing a hot glass rod through the opening in the Petri dish cover. A sample of the solution from the beaker was removed and analyzed spectrophotometrically. The buffer solution in the diffusion cell was withdrawn into a suction flask.

At zero time 20 ml. of the drug solution was pipetted into the diffusion cell. The delivery and the suction ends of the tubes from the pump were positioned in the diffusion cell as described earlier. The pump was then started.

Samples were removed from the solution in the beaker at regular intervals of time. In all cases, excepting the phenylalkylamines, these samples were analyzed immediately with the spectrophotometer. Samples of the drug solution from the reservoir were taken at various intervals during the course of the diffusion experiment. These samples were adequately diluted and analyzed spectrophotometrically. The temperature of the bath was monitored throughout the course of an experiment.

At the end of an experiment, the volume and pH of the solution in the beaker and the pH of the solution in the diffusion cell were measured. The pH values did not change throughout the course of an experiment for all studies.

A Typical Quasi-steady State Diffusion Experiment

A clean piece of Silastic membrane was clamped into position in the V-shaped quasi-steady state (see Fig. 4) diffusion cell. Each of the arms of the diffusion cell was filled with 100 ml. of phosphate buffer solution. The cell was then kept in a thermostated shaker bath for equilibration for about 8 - 10 hours. After this the solutions from both arms were withdrawn into a suction flask. Into one arm of the cell 50 to 100 ml. of phosphate buffer was added and at zero time an equal volume of the drug solution in phosphate buffer was added to the other arm. The open ends of the arms were covered with Parafilm.

At regular intervals of time, samples from both the arms of the diffusion cell were removed and analyzed for the drug spectrophotometrically. The experiment was continued until the difference between the absorbance measurements became very small. At the end of the experiment the volume and pH of the solutions in both arms were measured.

Diffusion of 4'-Aminopropiophenone Through Silastic Membrane

The solution of 4'-aminopropiophenone (PAPP) prepared in pH 6.8 phosphate buffer was used for both the steady state and quasi-steady state diffusion work. The solutions used on the desorption side of the membrane were 0.12 N HCl for the steady state diffusion and pH 6.5 phosphate buffer for the quasi-steady state diffusion experiments.

The steady state diffusion of PAPP from its saturated solutions through Silastic membrane was studied to determine the reproducibility of the results. The effects on diffusion of PAPP of ionic strength, concentrations of PAPP solutions, thickness of Silastic membranes and the hydrostatic pressure exerted on the membrane were studied.

Reproducibility of results.—The diffusion of PAPP from its saturated solution in pH 6.5 phosphate buffer through 3 mil thick Silastic membrane into 200 ml. of 0.12 N HCl at 37.5° was studied. The cell solution containing excess undissolved PAPP was agitated by bubbling nitrogen gas under pressure through it. The whole assembly was shaken in a thermostated shaker bath. Samples (1 ml.) of the beaker solution were removed every hour for about 8 - 10 hours. Each was diluted with 4 ml. of pH 6.8 phosphate buffer ($\mu = 0.3$) and the absorbance was measured at 307 mμ on the Beckman DU spectrophotometer. Five separate experiments were performed on each of the five days. Typical raw data for one such day are given in Table II.

Effect of hydrostatic pressure.—Solutions of PAPP in pH 6.8 phosphate buffer having same concentration were circulated into four diffusion cells. The suction tubes of the channels returning the solutions from the diffusion cells to the reservoir were adjusted at four different levels (see Fig. 5) in the stem of the diffusion cell. The levels of the tubes were 0, 1/2", 1" and 3" above the level of the solution in the beaker. The higher rate of pumping the solution from the cell to the reservoir over that of pumping the solution from the reservoir to the cell, kept the level in the cell constant at the level of the suction tube orifice. The rate of diffusion was monitored by spectrophotometric analysis of the samples from the beaker.

Effect of ionic strength.—A 100 ml. solution of 0.4 N HCl containing 2.5 g. of PAPP was prepared. Twenty ml. aliquots of this solution were added with 170, 330, 500 and 670 ml. of pH 6.8 phosphate buffer with an ionic strength of $\mu = 1.2$. The solutions were then diluted with distilled water to 2 liters to obtain solutions of PAPP of the same concentrations in phosphate buffer but with ionic strengths of 0.102, 0.198, 0.300 and 0.402 respectively. The pH values of these solutions were 6.69, 6.73, 6.75 and 6.78 respectively. These solutions were then circulated in four diffusion cells to study the diffusion of PAPP through Silastic membrane into 200 ml. of 0.12 N HCl at 23.0°.

Effect of thickness of membrane.—Silastic membrane was available in four different thicknesses of 3, 5, 10 and 20 mil. The diffusion of PAPP through these four thicknesses was studied at 24.90°. A solution of PAPP in pH 6.8 phosphate buffer from one reservoir containing about 8 liters of the solution was circulated through four cells, each one fitted with a Silastic membrane of different thickness. The samples of 0.12 N HCl from the beakers were analyzed as a function of time to monitor the rates of diffusion of PAPP.

Effect of temperature.—The diffusion of PAPP from its solution in pH 6.8 phosphate buffer through 3 mil thick Silastic membrane into 200 ml. of 0.12 N HCl was studied at seven different temperatures: 24.75°, 24.90°, 30.40°, 31.25°, 33.60°, 37.50° and 41.0°. At each temperature the diffusion was studied at four or more concentrations of PAPP in the phosphate buffer solutions. The same diffusion cells were used without changing the membranes to avoid any variation in membrane thickness and in area of the membrane available for diffusion. The temperature of the bath (American Instrument Company) was monitored throughout the diffusion experiment and was observed to hold constant within ± 0.25°.

Quasi-steady state diffusion of PAPP.—The diffusion of PAPP from its solution in pH 6.8 phosphate buffer through 5 mil thick Silastic membrane into an equal volume of pH 6.8 phosphate buffer was studied at 25.0°. The volumes of phosphate buffer solutions used - PAPP solution and phosphate buffer without any drug in it - in the two experiments were 50 and 100 ml.

Effect of pH on diffusion of PAPP.—The solutions of PAPP were prepared in 0.001 N, 0.01 N and 0.1 N HCl and pH 3.48, 4.38 and 5.47 acetate buffer and pH 6.70 phosphate buffer. The steady state diffusion of PAPP from these solutions through 3 mil thick Silastic membrane in 200 ml. of 0.12 N HCl was studied at 25.0°. The pH of the solutions were noted before and after the diffusion experiments and were observed to be unchanged. The absorbance of PAPP in the HCl solution in the beaker was measured as a function of time after 1:5 dilution with phosphate buffer. The absorbances of the solutions in the reservoirs, used for the circulation into the diffusion cells, were measured after appropriate dilutions with phosphate buffer.

Effect of ethanol on the rate of diffusion of PAPP.—The effect of ethanol on the steady state diffusion of PAPP through 3 mil thick Silastic membrane was studied at 25.0°. In one set of experiments identical percentages of ethanol were present in the solutions of PAPP in pH 6.8 phosphate buffer as well as in the 0.12 N HCl on the desorption side of the membrane. In another set of experiments ethanol was present in the phosphate buffer solution of PAPP but no ethanol was present in the HCl solution. In the third set of experiments ethanol was present only in the HCl solution on the desorption side of the membrane but no ehtanol was present in the phosphate buffer solutions of PAPP inside the diffusion cells.

Six flasks containing 500 ml. of pH 6.8 phosphate buffer (μ = 1.2) and 500 ml. of distilled water were added with 160, 320, 480, 640, 800 and 960 ml. of 95% ethanol and the volume in each flask was made up to 2 liters with distilled water. A solution of 3 g. of PAPP in 140 ml. of 0.3 N HCl was prepared. Twenty ml. of this solution was transferred to each of the six flasks containing ethanolic phosphate buffer solutions to obtain solutions of PAPP in phosphate buffer containing 7.5, 15.0, 22.5, 30.0, 37.5 and 45.0% V/V ethanol. Six 250 ml. volumetric flasks containing 15 ml. of 2 N HCl were added with 20, 40, 60, 80, 100 and 120 ml. of 95% ethanol and the volumes of the solutions were made up to 250 ml. to obtain 0.12 N HCl containing 7.5, 15.0, 22.5, 30.0, 37.5 and 45.0% V/V ethanol. Two hundred ml. of these ethanolic solutions was used in the diffusion experiment on the desorption side of the diffusion cells. The phosphate buffer solutions of PAPP containing corresponding concentration of ethanol were circulated into these diffusion cells.

In another set of experiments the 0.12 N HCl used on the desorption side of the diffusion cell contained 0, 10, 20, 30, 40 and 50% ethanol prepared as described before. The PAPP solution in the bulk volume of 8.5 liters was used for circulation into all six diffusion cells and did not contain any ethanol.

In the third set of experiments the diffusion of PAPP from its solution in phosphate buffer containing 18% ethanol through 3 mil Silastic membrane into 200 ml. of 0.12 N HCl containing no ethanol was studied. The concentration of PAPP in the ethanolic phosphate buffer solutions was varied from 1.87×10^{-3} M to 3.28×10^{-3} M.

The diffusion of PAPP from its saturated solutions in 0, 10, 20 and 30% ethanolic solution in water through 3 mil thick Silastic membrane into 0.1 N HCl containing 0, 10, 20 and 30% ethanol was studied at 24.25°.

The effect of ethanol on the quasi-steady state diffusion of PAPP was studied at 25.25°. Five hundred ml. solutions of PAPP in 0, 10, 20 and 30% ethanolic phosphate buffer were circulated in steady state diffusion cells fitted with 2.30 mil thick Silastic membrane (Fig. 5). The diffusion of PAPP from each of these solutions into 120 ml. of 0, 10, 20 and 30% ethanolic phosphate buffer was studied. The diffusion was monitored by measuring the absorbance of the samples of the external solution from the beaker at 307 mμ as a function of time. The samples were returned to the beakers. The loss of solutions from the beakers due to evaporation and repeated sampling was less than 2%.

Effect of ethanol on Silastic membrane.—Three steady state diffusion cells were filled with 0, 10 and 30% ethanolic phosphate buffer solutions and kept in 0.12 N HCl solutions containing the same concentrations of ethanol. After 15 hours the cells were emptied and washed with water, and the steady state diffusion of PAPP from one solution of PAPP in phosphate buffer circulated in all three cells was studied in absence of any ethanol, inside or outside the cell.

Diffusion of ethanol through Silastic membrane.—The steady state diffusion of ethanol through 3 mil Silastic membrane into 200 ml. of 0.12 N HCl was studied from absolute ethanol, from phosphate buffer solutions of PAPP containing 18% ethanol and from phosphate buffer solutions containing 10, 20, 30 40 and 50% ethanol.

Absolute ethanol was circulated into a diffusion cell fitted with a 3 mil Silastic membrane. About 0.5 ml. samples of 0.12 N HCl were removed at hourly intervals and 5 microliters of these samples were injected into a gas chromatograph for vapor phase analysis of ethanol. The percent ethanol present in the samples were calculated from a calibration curve.

The diffusion of ethanol from 18% ethanolic phosphate buffer solution containing increasing concentrations of PAPP from 1.87×10^{-3} $\underline{M}$ to 3.28×10^{-3} $\underline{M}$ through 3 mil Silastic membrane was studied at 24.60°.

The diffusion of ethanol from phosphate buffer solutions containing 10, 20, 30, 40 and 50% ethanol through a 3 mil thick Silastic membrane into 200 ml. of 0.12 $\underline{N}$ HCl was studied at 24.60°.

Effect of ethanol, propyl alcohol, isopropyl alcohol and t-butyl alcohol on diffusion of PAPP.—Three hundred grams of isopropyl alcohol, propyl alcohol and t-butyl alcohol were weighed and diluted with pH 6.8 phosphate buffer to 2000 ml. Similarly 240 ml. of ethanol was diluted to 2 liters with phosphate buffer. To each solution 20 ml. of a solution of 3.0 g. of PAPP in 120 ml. of 0.4 $\underline{N}$ HCl was added. The solutions were mixed and used for circulation in the steady state diffusion cells fitted with 3 mil Silastic membrane. The concentration of PAPP diffusing into 200 ml. of 0.12 $\underline{N}$ HCl was measured as a function of time.

Diffusion of 4'-Aminoacetophenone and 3'-Aminoacetophenone.

The diffusion of these two drugs through a 3 mil Silastic membrane from their solutions in pH 6.8 phosphate buffer into 120 ml. of 0.12 $\underline{N}$ HCl was studied at 25.0° and 37.5°. The concentrations of the drugs diffusing into HCl were measured spectrophotometrically after 1:5 dilutions with pH 6.8 phosphate buffer.

Diffusion of Barbituric Acid Derivatives

The steady state diffusions of barbituric acid derivatives - amobarbital, barbital, butabarbital, cyclobarbital, diallylbarbituric acid, mephobarbital, metharbital, pentobarbital, phenobarbital, secobarbital, thiopental and thiamylal - through 3 mil Silastic membrane from their solutions in pH 4.7 acetate buffer into pH 10.1 borate buffer were studied at 25.0° and 37.5°.

Weighed amounts of barbituric acid derivatives were dissolved in small volumes of 1 N NaOH and immediately diluted with pH 4.7 acetate buffer solution to 2 liters to obtain solutions which were approximately 5×10^{-3} M in thiamylal, thiopental and mephobarbital and 5×10^{-3} M in the remaining barbituric acid derivatives. These were used as reservoir solutions and circulated through the diffusion cells fitted with 3 mil Silastic membranes. The solutions used on the desorption side of the membrane in the beakers were 200 ml. of pH 10.1 borate buffer. The samples of borate buffer from the beaker were removed at regular intervals of time. Their absorbances were measured on the Beckman DU spectrophotometer without any treatment. After measuring their absorbances, the samples were returned to the beakers.

The steady state diffusion of barbital and pentobarbital through 3 mil Silastic membrane was also studied from their solutions in acetate, phosphate and borate buffer solutions of different pH values at 37.5°. Solutions of barbital in pH 4.70 acetate buffer, pH 6.65, 7.30, 7.60 and 8.12 phosphate buffer and pH 9.15, 9.75 and 10.55 borate buffer solutions were used. Solutions of pentobarbital in pH 4.60 acetate buffer, pH 6.99, 7.57, 7.90 and 8.18 phosphate buffer and 8.65, 9.05 and 9.53 borate buffer solutions were used.

Diffusion of Phenylalkylamines

The solutions of α-methylphenethylamine hydrochloride, 2-amino-4-methyl-4-phenylpentane hydrochloride, 3-amino-1-phenylbutane sulfate, 1-methyl-5-phenylpentylamine hydrochloride and α-ethylphenethylamine hydrochloride in pH 8.93, 9.45, 9.40, 9.60 and 9.28 borate buffer respectively were used for the diffusion work. The steady state diffusion of these substances through 3 mil Silastic membrane into 120 ml. of pH 6.8 phosphate buffer was studied at 25.0°. Samples of the phosphate buffer solutions (1 ml.) were removed every 15 minutes and stored in a refrigerator. All the samples were analyzed simultaneously with the standard solutions for the preparation of the calibration curve.

Diffusion of Dextromethorphan and Progesterone

The steady state diffusion of dextromethorphan from solutions in peanut oil, mineral oil and pH 10.1 borate buffer through 3 mil Silastic membrane into pH 6.8 phosphate buffer was studied at 37.5°. Similarly steady state diffusion of progesterone from a solution in peanut oil and a saturated solution in phosphate buffer through 3 mil Silastic membrane into pH 6.8 phosphate buffer was studied at 37.5°.

The solutions of the two compounds in peanut oil were prepared by dissolving an accurately weighed amount of each drug in an accurately weighed amount of peanut oil. The density of the peanut oil was determined by weighing 10 ml. of peanut oil in a 10 ml. volumetric flask. The volumes of the peanut oil used for the preparation of the solutions were then calculated from the knowledge of the weights and the density of the peanut oil. The molarities of dextromethorphan and progesterone in the peanut oil solutions were then calculated.

The diffusion of dextromethorphan was also studied from its saturated solutions in peanut oil and mineral oil. The concentration of dextromethorphan in peanut oil was determined by diluting a weighed amount of the filtered solution with chloroform and measuring the absorbance of the solution at 277 mμ against a chloroform blank containing an equivalent amount of peanut oil. The ϵ value of dextromethorphan in peanut oil diluted with chloroform was determined the same way using the solution of dextromethorphan in peanut oil containing a known weight of the drug. The ϵ value of dextromethorphan in mineral oil was determined by dissolving an accurately weighed quantity of dextromethorphan in mineral oil and measuring its absorbance against a mineral oil blank. The saturated solution of the drug in the mineral oil was filtered. Its absorbance was measured and the concentration in the solution was calculated from the knowledge of the ϵ value.

Diffusion of Drugs Through Silastic Capsules

Silastic capsules (Dow Corning Center for Aid to Medical Research) were small Silastic pouches prepared by sealing pieces of tubes (about 6 mm. in diameter x about 2.4 cm. in length) at both ends. These were cleaned externally with water and dried in air.

To determine the area available for diffusion five capsules were cut open at their sealed ends. The resultant tubes were cut again on one side to obtain flat sheets of the capsule material. The thickness of this capsule material was measured with a micrometer screw as described previously. The material was then cut into small pieces and inserted into 10 ml. graduated cylinder containing 5 ml. of water. The volume of water displaced by the material from the five capsules was measured. The average volume of Silastic material from one capsule was then calculated from the volume of the water displaced by material from five capsules. The area of the Silastic membrane of one capsule was then obtained by dividing the volume of the Silastic material from one capsule by the thickness of the Silastic material.

Saturated solutions of 4'-aminopropiophenone in phosphate buffer, solutions of barbital, pentobarbital and phenobarbital in acetate buffer and solutions of dextromethorphan in borate buffer, peanut oil, and mineral oil were prepared. The Silastic capsules were cut open at one corner and were filled with these saturated solutions. The hole in each of the capsules was sealed by forcing a portion of Silastic medical grade adhesive type A (Dow Corning Center for Aid to Medical Research) into and around the hole. The capsules were set aside for one day and were tested for leaks by pressing them lightly between fingers. Similarly capsules containing solvents without drugs were also prepared.

The capsules containing barbital, pentobarbital and phenobarbital were washed with water and put in 50 ml. of pH 10.1 borate buffer in glass vials. These vials were preequilibrated at 37.5° for about 10 hours. Similarly capsules of 4'-aminopropiophenone and dextromethorphan were put in glass vials containing 50 ml. of 0.12 N HCl and pH 6.8 phosphate buffer respectively. The samples from the vials were assayed spectrophotometrically for the respective compounds.

RESULTS

Screening of Permeability of Polymer Films

The spectrophotometric cruves obtained on the Cary recording spectrophotometer were checked for the peaks characterizing the compounds under study. This method of analysis was sensitive to 1×10^{-4} M concentration in all cases and much more sensitive in the case of steroids (Table I).

Polyethylene membrane is permeable to 4'-aminoacetophenone in aqueous solutions and in peanut oil, and to 4'-aminopropiophenone in ethylene glycol. Both compounds permeate Rilsan membrane from ethanolic solutions. Polypenco membrane is permeated by 4'-aminopropiophenone and 3'-aminoacetophenone from their solutions in 0.1 N NaOH and ethanol. Polypropylene is nonpermeable to all the drugs tested. Substances were leached by phosphate buffer from cellulose triacetate and cellulose butyrate membranes and interfered with the spectrophotometric analyses of the drugs. After compensating for the absorbances of these interfering substances, it was concluded that 4'-aminopropiophenone permeated cellulose triacetate from solutions in propylene glycol, ethanol and polyethylene glycol 200. Positive results were recorded also for barbital in polyethylene glycol 200 and sulfabenzamide in ethanol. Mylar polyester film was available only in small quantity and was impermeable to all the drugs tested with the available films. Silastic membrane was permeable to 4'-aminopropiophenone from solutions in all the solvents tested except mineral oil, to 3'-aminoacetophenone from all solvents except HCl and mineral oil, to progesterone from ethanol, to barbital from ethanol and ethylene glycol and to phenobarbital from peanut oil, ethanol, polyethylene glycol 200, phosphate buffer and 0.1 N HCl. Since the purpose of this screening was to search for a membrane which would allow permeation of a majority of compounds in measurable quantities only Silastic membrane was investigated further.

Solubility Studies

The solubilities of barbituric acid derivatives in pH 4.7 acetate buffer at 25.0° are reported in Table III. The solubilities of aminoalkylphenones in pH 6.8 phosphate buffer at 37.5° are given in Table IV. The solubility of 4'-aminopropiophenone in phosphate buffer containing various percentages of ethanol were interpolated from Fig. 6 showing the relation between solubility and percent ethanol. The solubility values are given in Table V.

The solubilities of phenylalkylamines in 0.1 N NaOH could not be determined because the insoluble liquid amines formed an emulsion which could not be broken even after extended periods of centrifugation. Clear solutions of these compounds for the determination of the solubilities were not obtainable.

Partition Coefficients

The partition coefficients for barbituric acid derivatives between their solutions in acetate buffer and chloroform presaturated with each other are reported in Table III. The partition coefficients for 4'-aminopropiophenone, 4'-aminoacetophenone, and 3'-aminoacetophenone between their solutions in pH 6.8 phosphate buffer and chloroform presaturated with each other at 25.0° are given in Table IV. The partition coefficient between phosphate buffer solutions of 4'-aminopropiophenone containing ethanol and organic solvents were not obtained because of the high solubility of ethanol in most organic solvents.

Thickness of Membranes

The results obtained from the measurements of the membrane thickness are recorded in Table VI. The results were analyzed statistically (94) as shown in Appendix C - VI for 3 mil thick Silastic membranes. The coefficients of variation (94) and the limits within which the mean thicknesses vary have been reported at 95% confidence levels (94) in Table VI.

Permeability of Silastic Membranes to Phosphate Buffer Salts and Hydrochloric Acid Solution

The ammonium molybdate reagent solution (92) gave a yellow colored solution when mixed with an equal volume of 4.8×10^{-4} M solution of phosphate buffer. A faintly yellow colored solution was obtained with 9.60×10^{-6} M phosphate buffer solution. The sample from the diffusion cell kept for 15 hours in a beaker containing phosphate buffer, did not yield a precipitate or a colored solution with this reagent. It was therefore concluded that phosphate buffer salts do not diffuse significantly through Silastic membrane.

A white turbid solution was obtained when 4×10^{-5} $\underline{M}$ solution of HCl was acidified with nitric acid and an equal volume of 10% silver nitrate solution was added. A sample from the diffusion cell kept for 11 hours in a beaker containing 0.1 $\underline{N}$ HCl did not yield a turbid solution when treated similarly. Also, the 6.45 pH of the solution in the cell was constant for the time interval. It was therefore concluded that HCl does not diffuse significantly through Silastic membrane.

Treatment of Data

Table II shows the raw data obtained on the steady state diffusion of 4'-aminopropiophenone from solutions in pH 6.5 phosphate buffer through 3 mil Silastic membrane into 200 ml. of 0.12 $\underline{N}$ HCl at 37.3°. This and other such data were plotted according to the integrated form of Eq. 9

$$A = D\,S\,K\,t = D\,S\,(C_2 - C_1)\,t\,/\,X \qquad \text{(Eq. 24)}$$

where A is the amount in moles diffused in t seconds through a membrane of X cm. thickness and S cm.^{2} area. K is the concentration gradient $(C_2 - C_1) / X$. D is the apparent diffusion constant in cm.^{2}/sec. and C_2 is the concentration of the compound in the cell. C_1 is the concentration of the compound on the desorption side of the membrane. In the steady state diffusion experiments the concentration C_1 was maintained zero by keeping the diffused species charged in the solution in the beaker. Thus 0.12 N HCl in the case of 4'-aminopropiophenone and other aminoalkylphenones, pH 10.1 borate buffer in the case of barbituric acid derivatives and pH 6.8 phosphate buffer in the case of phenylalkylamines and dextromethorphan kept the respective diffusates in the charged form. Charged species do not diffuse through Silastic membrane. Hence the concentration C_1 in the beaker was always zero with respect to the diffusing species.

When the concentration of the solution in the beaker was plotted against time in hours, the slope of the plot was

$$\text{slope} = D\ S\ C_2\ /\ X\ V = dC/dt \qquad \text{(Eq. 25)}$$

where V was the volume of the solution in the beaker. Since all the terms in Eq. 25 are known except the apparent diffusion constant D, it can be calculated from the value of the slope.

The quasi-steady state diffusion data were treated according to Eq. 21. Since the volumes V_1 and V_2 used in the two arms of the quasi-steady state diffusion cell were equal, Eq. 22

$$(X\ V\ /\ 0.869\ S)\ \log\ (C_2 - C_1\ /\ C_0) = -D\ t \qquad \text{(Eq. 22)}$$

was used. The plot of $-\log\ (C_2 - C_1\ /\ C_0)$ against time yields a slope of $0.869\ S\ D\ /\ X\ V$ from which D, the apparent diffusion constant, can be calculated.

Diffusion of 4'-Aminopropiophenone Through Silastic Membrane

Reproducibility of results.—The regression analysis of the raw data on the diffusion of 4'-aminopropiophenone (PAPP) in the replicate five runs of Table II is given in Appendix C - VII. The intercepts obtained by regression analysis were tested by the "student" t-test (94, 95, 96) to ascertain the validity of the hypothesis that the intercepts were zero. In all five cases the hypothesis that the intercepts were zero could not be rejected at the 95% confidence level. Hence it was concluded that the plots of the concentration of the diffused material versus time go through the origin. The coefficient of variation for values among the slopes was 6.98%.

The slopes of the concentration versus time plots for five replicate diffusion experiments on each of five days at 37.5° are noted in Appendix C - VIII. The concentration of PAPP in the saturated solutions used for the experiments was kept constant at 2.35×10^{-3} M. The slopes were analyzed statistically (94, 95, 96) (Appendix C - VIII) to test the hypothesis that there was no significant difference between the slopes on the same day and between the slopes on different days. An analysis of variance table was constructed and by the "F" test it was concluded that the slopes obtained within and among days were statistically equal. The coefficient of variation for means of the slopes on different days was 6.09%.

Ionic strength effect.—The data obtained from the steady state diffusion experiments for the concentrations of PAPP diffusing through Silastic membrane from phosphate buffer solutions with ionic strengths of 0.102, 0.198, 0.300 and 0.402 were plotted against time. The slopes of these plots were normalized by dividing by the concentrations of the diffusing solutions. The mean of these resultant specific rates of diffusion was $(7.13 \pm 0.23) \times 10^{-2}$ (Appendix C - IX).

The coefficient of variation was 3.24%. This value of the coefficient of variation is well within the value of 6.98% calculated for the variation in slopes from five replicates of an experiment on one day. This indicates that the ionic strength has no significant effect on the diffusion of PAPP through Silastic membrane.

Effect of hydrostatic pressure.—The values of the slopes of the concentration of PAPP diffused versus time in the steady state diffusion experiments were normalized with respect to the concentration of the drug as shown in Appendix C - X. The values of the specific rates of diffusion so obtained were very close to each other. The coefficient of variation was 1.45%. This value being less than the coefficient of variation calculated for replicates of a diffusion experiment on one day, it was concluded that the hydrostatic pressures exerted by the liquids within the limits of the levels studied, have no significant effect on the rate of diffusion of PAPP through Silastic membrane.

Effect of thickness of membrane on the specific rate of diffusion.—The plots of the concentration of PAPP diffused in steady state diffusion experiment through Silastic membrane versus time as a function of membrane thickness are shown in Fig. 7. Equation 25 may be rewritten as

$$D / X = \text{Slope} \times V / S\, C_2 \qquad \text{(Eq. 26)}$$

Thus the slopes of the plots of concentration of diffused drug versus time may be normalized as

$$D / X = \text{slope} \times 0.200 / 10.40 \times 1.517 \times 10^{-3} \times 3600 \qquad \text{(Eq. 27)}$$

where 0.200 liter is the volume of the solution, 10.40 cm.^{2} is the area, 1.517×10^{-3} is the molar concentration of PAPP and 3600 is the factor for converting hours to seconds. The normalized values of the slopes, specific rates of diffusion, are given in Table VI. When these specific rates of diffusion are plotted against the reciprocal of thickness of the membranes, a straight line is obtained as shown in Fig. 8. The slope of this line, $3.76 \pm 0.19 \times 10^{-10}$ cm.^{2}/sec. is the apparent diffusion constant D for the diffusion of PAPP through Silastic membrane at 24.90°.

Effect of concentration on the rate of diffusion.—The slopes of the plots of concentration of PAPP diffused through Silastic membrane versus time are listed in Table VII as a function of concentration and temperature. These rates of steady state diffusion were plotted against the respective concentrations at each temperature. Fig. 9 shows such plots at three temperatures. The slopes of these plots are the specific rates of diffusion of PAPP through Silastic membrane and are equal to D S / X V and are given in Table VII. The apparent diffusion constants calculated from these values are also given in Table VII. These values were calculated using the equation

$$D = \text{slope} \times X \times V / S = \text{slope} \times 7.52 \times 10^{-3} \times 0.200 / 10.40 \times 3600 \qquad \text{(Eq. 28)}$$

where 0.200 liter is the volume V, 10.40 cm.^{2} is the area S, 7.52×10^{-3} cm. is the thickness X and 3600 is the factor for converting hours to seconds.

Effect of temperature on the rate of diffusion.—The effect of temperature on the rate of steady state diffusion of PAPP through

3 mil thick Silastic membrane is shown in Fig. 9. The apparent diffusion constants at seven temperatures are recorded in Table VII. Figure 10 shows the plot of logarithm of the apparent diffusion constants versus the reciprocal of the absolute temperatures. From the slope of this plot the activation energy of diffusion ΔEa can be calculated using the equation

$$\log D = \log D_0 - \Delta Ea / 2.303\ R\ T \qquad \text{(Eq. 29)}$$

ΔEa for PAPP diffusion through Silastic membrane was calculated to be 4.90 Kcal./mole.

Quasi-steady state diffusion.—The plots of $-\log\ (C_2 - C_1/C_0)$ versus time for quasi-steady state diffusion of PAPP through 5 mil Silastic membrane are shown in Fig. 11. The apparent diffusion constants were calculated from the slopes of these plots to be 3.93×10^{-10} and 3.94×10^{-10} cm.^{2}/sec. for 50 ml. and 100 ml. volumes of the solutions in the arms of the diffusion cell at 25.0°. These values are within the estimated interval for diffusion constants - $3.76 \pm .19 \times 10^{-10}$ cm.^{2}/sec. - obtained from steady state diffusion experiments.

Effect of pH on the rates of diffusion.—The apparent diffusion constants obtained for the diffusion of PAPP from the solutions of various pH values through 3 mil Silastic membrane have been reported in Table VIII. The D - pH profile constructed from the values reported in Table VIII is shown in Fig. 12. The apparent diffusion constant approaches an asymptotic value of 3.66 at higher pH values. The pH corresponding to half the asymptotic value of 1.83 is 2.45 which is the pK_a of the drug obtained from the diffusion experiments.

The pK_a of the drug obtained spectrophotometrically is 2.42. (Table I)

Effect of ethanol on the rate of diffusion of 4'-aminopropiophenone.—The results obtained in the steady state diffusion of PAPP through 3 mil Silastic membrane are recorded in Table IX. Set A in Table IX lists the rates of diffusion when ethanol is present on both sides of the membrane in equal concentration. A decline in the specific rate of diffusion was observed with the increase in the concentration of ethanol present in contact with PAPP. The plots of the absorbance of the diffused PAPP versus time for different concentrations of ethanol in PAPP solution are shown in Fig. 13. Set D in the Table IX shows the same results obtained with saturated solutions of the drug in aqueous ethanol and 0.1 N HCl containing the same concentration of ethanol. In set B the diffusion constants and the specific rates of diffusion are invariant for the different concentrations of ethanol present in HCl solution. Set C shows that when the concentrations of the drug are varied in solutions with a constant concentration of ethanol, the specific rates of diffusion with respect to the concentration, and the apparent diffusion constants are invariant.

The data obtained from quasi-steady state experiments were treated according to

$$V_2/(K_{p2}V_1 + K_{p1}V_2)\ln[K_{p2}C_0/K_{p2}C_0 - C_1(K_{p2}V_1 + K_{p1}V_2)/V_2] = D'St/XV_1 \quad \text{(Eq. 30)}$$

where subscripts 1 and 2 refer to the compartments containing solutions without PAPP and with PAPP respectively at zero time. V_1 and V_2 are the volumes of the solutions with PAPP concentrations of C_1 and C_2

respectively. K_{p1} and K_{p2} are the apparent partition coefficients between membrane material and aqueous solutions in the two compartments. Equation 30 has been derived in Appendix C - III.

When the numerator and the denominator of the logarithmic term in Eq. 30 are multiplied by the intrinsic diffusion constant D' for diffusion within the membrane alone, the resultant equation after rearrangement of terms becomes

$$\ln[D'K_{p2}C_0V_2/D'K_{p2}C_0V_2 - C_1(D'K_{p2}V_1 + D'K_{p1}V_2)] = (D'K_{p2}V_1 + D'K_{p1}V_2)St/XV_1V_2 \qquad \text{(Eq. 31)}$$

If $K_{p1} = K_{p2} = K_p$ as is the case when the concentration of ethanol on both sides of the membrane is the same, Eq. 30 reduces to

$$\ln[C_0V_2/(C_0V_2 - C_1(V_1 + V_2)] = D\ S\ t(V_1 + V_2)/XV_1V_2 \qquad \text{(Eq. 32)}$$

where D is the apparent diffusion constant, $D'K_p$. The apparent diffusion constants of PAPP for diffusion from 0, 10, 20 and 30% ethanolic phosphate buffer into ethanolic phosphate buffer of the same composition were calculated from the slopes of the plots of logarithmic term in Eq. 32 versus time and their values are given in set A of Table X.

These values of $D'K_p$ were used in places of $D'K_{p1}$ and $D'K_{p2}$ in Eq. 31 for comparable compositions of ethanolic phosphate buffers. These values of $D'K_{p1}$ and $D'K_{p2}$ were used to determine the slope $(D'K_{p2}V_1 + D'K_{p1}V_2)S/XV_1V_2$, from the plot of the calculated left hand term of Eq. 31 versus time for various concentrations of ethanolic phosphate buffer on the two sides of the Silastic membrane. The values of $D'K_{p1}V_2 + D'K_{p2}V_1$ derived from the measured slopes and calculated from the known values of $D'K_{p1}$, $D'K_{p2}$, V_1 and V_2 are given in Table X for purposes of comparison.

The specific rates of diffusion of ethanol from phosphate buffer containing 18% ethanol and different concentrations of PAPP were found to be independent of the drug concentration (Table XI). The specific rates of diffusion of ethanol from different concentrations of ethanol in phosphate buffer are also reported in Table XI.

The specific rates of diffusion of PAPP from solution in phosphate buffer through Silastic membrane pretreated with ethanol solutions of different concentrations was observed to be the same in all cases indicating that the membrane is not altered physically by ethanol; and that the alteration, if any, is reversible.

Effect of ethanol, propyl alcohol, isopropyl alcohol and t-butyl alcohol on the diffusion of 4'-aminopropiophenone.—The concentrations of all the alcohols in the phosphate buffer were 2 M. The specific rates of diffusion of PAPP from solutions containing above listed alcohols were 5.05, 5.95, 6.41 and 5.12 × 10^{-3} $hr.^{-1}$ respectively. It was therefore concluded that all four alcohols modify the rate of diffusion of the drug to the same extent.

Diffusion of 4'-Aminoacetophenone and 3'-Aminoacetophenone

The apparent diffusion constants for the steady state diffusion of these two drugs through 3 mil Silastic membrane from solutions in pH 6.8 phosphate buffer into 0.12 N HCl have been reported for two temperatures of 25.0° and 37.5° in Table IV. (see also Fig. 10) Table IV also lists the apparent diffusion constants for 4'-aminopropiophenone, the partition coefficients of these three drugs and their solubilities together with the activation energies of diffusion.

Diffusion of Barbituric Acid Derivatives

The apparent diffusion constants and the specific rates of steady state diffusion of amobarbital, barbital, butabarbital, cyclobarbital, diallylbarbituric acid, mephobarbital, metharbital, pentobarbital, phenobarbital, secobarbital, thiamylal, and thiopental through 3 mil Silastic membrane from acetate buffer solutions are given in Table XII for two temperatures 24.60° and 37.5°. The plots of the concentration of diffused drugs against time have been shown in Figs. 14 and 15.

The apparent diffusion constants for the steady state diffusion of barbital and pentobarbital from solutions of different pH values through Silastic membrane are reported in Table XIII. The plots of apparent diffusion constants versus pH for the two drugs are shown in Fig. 16. From these plots the pK_a values of barbital and pentobarbital were calculated to be 7.50 and 7.72 respectively. The pK_a values of these two drugs obtained titrimetrically were 7.45 and 7.65 respectively.

The plots of the logarithm of apparent diffusion constants for some of these compounds against the reciprocal of the absolute temperatures have been shown in Fig. 17. The activation energies of diffusion ΔEa for barbituric acid derivatives have been reported in Table XII.

Diffusion of Phenylalkylamines

The apparent diffusion constants and the specific rates of diffusion from the steady state diffusion of α-methylphenethylamine, 3-amino-1-phenylbutane, 1-methyl-5-phenylpentylamine, α-ethylphenethylamine and 2-amino-4-methyl-4-phenylpentane from their solutions in borate buffer at pH values of 8.93, 9.40, 9.60, 9.28 and 9.45 through 3 mil Silastic membrane into 200 ml. of pH 6.8 phosphate buffer are reported in Table XIV. The plots of absorbance of the drug diffused versus time are shown for three drugs in Fig. 18. The concentrations given in Table XIV are the total concentrations and the concentrations of the uncharged species calculated from the equation (97) where the pK_a values are given in the table.

$$pH = pK_a + \log [base] / [salt] \qquad \text{(Eq. 33)}$$

Diffusion of Dextromethorphan and Progesterone

The data obtained in the steady state diffusion study of dextromethorphan were plotted as concentration of the drug diffusing from solutions in peanut oil, mineral oil and pH 10.1 borate buffer through 3 mil Silastic membrane into phosphate buffer versus time as shown in Fig. 19. The apparent diffusion constants calculated from these plots are given in Table XV.

The diffusion of progesterone was studied using a steady state diffusion cell and the data obtained were plotted as shown in Fig. 20. It is observed from Fig. 20 that the concentrations of progesterone approach asymptotic values in the two plots. The pH adjustment of the solution on the desorption side of the membrane to force the steady state diffusion conditions was not possible as progesterone does not have a pK_a. The data obtained were therefore treated by the quasi-steady state equation, (Appendix C - IV) using the equilibrium concentration values. The apparent diffusion constants calculated for progesterone are given in Table XVI.

Diffusion of Drugs from Silastic Capsules

The average area of Silastic membrane in the capsule was found to be 5.58 $cm.^2$. The average membrane thickness was 3.134×10^{-2} cm. The adhesive sealed the capsules well as tested for their airtightness by pressing between fingers. However the portion of the adhesive spread over a large part of the capsule making thickness at those places different from average thickness of the capsule membrane.

The apparent diffusion constants and the specific rates of diffusion obtained for the diffusion of barbital, phenobarbital, pentobarbital from saturated solutions in acetate buffer, for 4'-aminopropiophenone from saturated solution in phosphate buffer and for dextromethorphan from saturated solutions in borate buffer, peanut oil and mineral oil are given in Table XVII.

DISCUSSION

Permeability of Silastic Membrane

Silastic membrane is impermeable to chloride ions and phosphate buffer salts. The apparent diffusivities of 4'-aminopropiophenone, pentobarbital and barbital (Figs. 12 and 16) decrease with decreased concentrations of uncharged species in the solution. Increased concentrations of charged species on the desorption side of a Silastic membrane had no effect on the rate of transfer of the uncharged species through the membrane. This has been shown for all the compounds studied, e.g. the rate of transfer of dextromethorphan (pK_a = 8.25) from saturated solution in borate buffer or mineral oil was invariant with increasing concentrations of protonated dextromethorphan in the phosphate buffer on the other side of the membrane (Fig. 19). In fact, the concentrations of dextromethorphan on the desorption side of the membrane greatly exceeded the total concentration on the diffusing side.

Progesterone does not have a pK_a and cannot exist as a charged species. The effect of decreased concentration gradient with increase in the concentrations in the solution on the desorption side is apparent from the approach to an asymptotic concentration (Fig. 20).

These facts demonstrate that Silastic membrane is impermeable to charged molecules. This phenomenon was used to force steady state conditions in the diffusion experiments throughout this investigation.

Fick's Law of Diffusion

The observed effects of the concentrations of 4'-aminopropiophenone (PAPP) solutions and the thickness of Silastic membrane on the diffusion of PAPP were in accordance with Fick's law of diffusion

$$dA/dt = D\ S\ dC/dx \qquad \text{(Eq. 4)}$$

where A is the amount in moles diffused in time t through a membrane with surface area of S cm.^{2}. The differential dC/dx is the concentration gradient and D is the apparent diffusion constant. Under the steady state conditions where the concentration of the diffusable species on the desorption side of the membrane is essentially zero, Eq. 4 becomes

$$D/X = dC/dt\ (V/SC_2) \qquad \text{(Eq. 34)}$$

where dC/dt is the slope (Eq. 26) of the linear plot of the concentration of PAPP appearing on desorption side of the membrane with time (Fig. 7), V is the volume and C_2 is the concentration of PAPP in solution from which the diffusion is occuring. The linearity of such plots indicate that the specific rate of diffusion, D/X, is inversely proportional to the thickness of the membrane. The validity of this relationship is shown by the linearity and zero intercept of the plot in Fig. 8.

The effect of concentration of PAPP on the rate of diffusion is shown in Fig. 9 and is in accordance with Eq. 25 rewritten as

$$dC/dt = DSC_2/XV \qquad \text{(Eq. 35)}$$

which states that the rate of diffusion is directly proportional to the concentration of diffusing species provided that the concentration is zero on the desorption side of the membrane.

Effect of pH on Diffusion

The plot of the apparent diffusion constant D versus pH of the diffusing solution is shown in Fig. 12 for PAPP and in Fig. 16 for barbital and pentobarbital. The apparent diffusion constants were calculated by Eq. 24 where C_2 was the total concentration and included both charged and uncharged species. These apparent diffusion constants decrease with decreased concentrations of the uncharged species in the solution since Silastic membrane is impermeable to charged species. The pK_a values of barbital and pentobarbital were the pH at the mid-point of the sigmoid curve of apparent diffusion constants versus pH (Fig. 16). The pK_a of PAPP was the pH at half the asymptotic value in sigmoidal curve of apparent diffusion constants versus pH (Fig. 12).

Apparent Diffusion Constants From Steady and Quasi-steady State Diffusion Experiments

The value of the apparent diffusion constants (D in Eq. 24) for the steady state diffusion of uncharged 4'-aminopropiophenone (PAPP) through Silastic membrane at 25.0° is $(3.76 \pm 0.19) \times 10^{-10}$ cm.^{2}/sec. These results have been shown to be highly reproducible (Appendix C - VIII). The apparent diffusion constant (D in Eq. 22) obtained for the same compound at the same temperature from quasi-steady state diffusion experiment was 3.94×10^{-10}cm.^{2}/sec. This value lies within the confidence interval calculated for the apparent diffusion constants for the steady state diffusion data. The coincidence of the apparent diffusion constants obtained from the two different methods shows the validity of the results.

Non-dependence of Apparent Diffusion Constants of Drugs on Molecular Weights

The diffusion constants for the diffusion of a substance in an isotropic medium has been related to molecular weight in several equations e.g. Eqs. 1 and 2. Barrer and Chio (98) have simplified these relations, lumping together the constants, to

$$D = a\ M^{b} \qquad \text{(Eq. 36)}$$

where D is the diffusion constant, a and b are arbitrary constants and M is the molecular weight. They have claimed that this expression holds moderately well for the diffusion of inert gases through silicone membranes.

The diffusion of barbituric acid derivatives through Silastic membranes was studied to test this relationship. The apparent diffusion constants (Table III) were plotted against the cube root and square root of the molecular weights of the respective compounds according to Eqs. 1 and 2 respectively. Similarly, the logarithm of the apparent diffusion constants of barbituric acid derivatives (Table III) and those of the other compounds (Tables IV and XIV) were plotted against the logarithm of their molecular weights in accordance with the logarithmic transformation of Eq. 36. The points were too scattered to permit any assumption of correlation between molecular weights and the apparent diffusion constants.

Barrer et al. (99) have shown that the diffusion of hydrocarbons in silicone rubber is "less sensitive to size and shape of the penetrant molecule, and thus silicone rubber is less selective than natural rubber as a separation medium." Their data presented for the diffusion of hydrocarbons in silicone rubber did not permit correlation with the molecular weights of the compounds.

Postulated Mechanism of Transport in Silastic Membrane

The transport of compounds from a solution into a membrane, through the membrane and then into another solution has been shown to obey Fick's law of diffusion. The transfer of compounds from the solution into the membrane must be non-rate determining in the concentration range studied. Fick's law with its dependence on membrane thickness and concentration gradient fully describes the transport process from very low to saturation concentrations of PAPP. The diffusion constants obtained from the steady state and the quasi-steady state experiments are equal.

The non-dependence of the apparent diffusion constants on the molecular weights of the diffusing species may be explained on the basis of a partition hypothesis. In the partition hypothesis, the non-charged diffusing species partitions from the solution into the adjacent membrane monolayer, is transported across the membrane and then repartitioned into the solution on the other side of the membrane. The partitionings on either side of the membrane are rapidly effected.

Apparent Diffusion Constants and Partition Coefficients

The partition hypothesis states that the apparent diffusion constant D is related to the partition coefficient K_p

$$D = D'K_p \qquad \text{(Eq. 37)}$$

as may be readily seen from Eqs. 17 and 20 where D' is the intrinsic diffusion constant for a compound in Silastic membrane.

This hypothesis was tested by plotting (Fig. 21) the apparent diffusion constants of barbituric acid derivatives against their coefficients of partition between chloroform and acetate buffer solutions (Table III). A fairly good straight line could be drawn through the points. This linear relationship implies that the partition coefficients of all the barbituric acid derivatives between Silastic membrane and the acetate buffer are linearly related to the partition coefficients between chloroform and acetate buffer. It assumes that the intrinsic diffusion constant D' is the same for all the barbituric acid derivatives in the Silastic membrane. These assumptions may be reasonably true for compounds belonging to a homologous series. However not all the barbituric acid derivatives studied belong to such a series. Hence the deviations of the few compounds (Fig. 21) from the linear plot are to be expected. The diffusion constants of thiamylal and thiopental are extremely high, commensurate with their high partition coefficients (Table III).

The partition hypothesis is further substantiated by the good linear plot (Fig. 22) of diffusion constants against the coefficients of partition of aminoalkylphenones between chloroform and phosphate buffer solutions (Table IV).

Apparent Diffusion Constants and Solubilities

The partition coefficient may be defined as the ratio of the activities and/or solubilities of a compound in two phases (100).

$$K_p = C_m/C_a = S_m/S_a \qquad \text{(Eq. 38)}$$

where K_p is the partition coefficient, C_m and C_a are the concentrations of a compound in membrane and the aqueous buffer solution respectively, and S_m and S_a are the solubilities of the compound in the membrane and the aqueous buffer solution respectively. When Eq. 38 is substituted into Eq. 37 the resultant equation obtained is

$$D = D' \; S_m/S_a \qquad \text{(Eq. 39)}$$

Barbituric acid derivatives do not significantly partition into silicone liquid 200 from acetate buffer solutions. The estimates of partition coefficients between the two solvents was in great error. When the solubilities and the intrinsic diffusion constant D' of barbituric acid derivatives in Silastic membrane are assumed to be equal, the product $D'S_m$ in Eq. 39 will be constant. The plot of the apparent diffusion constants against the reciprocal of the solubilities of barbituric acid derivatives in acetate buffer (Table III) show a reasonably linear correlation (Fig. 23). The deviations of some points from the straight line relationship are to be expected since the simplifying assumptions of constancy of solubility and intrinsic diffusion constant in Silastic membrane are not rigidly true in all cases.

The phenylalkylamine series of drugs were diffused through Silastic membrane to confirm the relationship between apparent diffusion constants (Table XIV) and partition coefficients, and solubilities of the drugs. Unfortunately the ease of emulsification of the liquid amines prevented the ready estimates of the solubilities and the partition coefficients of this series of drugs.

Effect of Ethanol on Diffusion of 4'-Aminopropiophenone Through Silastic Membrane

The results of the steady state diffusion of PAPP from ethanolic phosphate buffers (Table IX) demonstrate that the rate of diffusion of PAPP decreases with increased concentration of ethanol in contact with the drug (Table IX, Set A). The rate of diffusion is invariant with different concentrations of ethanol in the HCl solution on the desorption side of the membrane (Table IX, Set B). However, the rate is slightly but significantly higher than that in complete absence of ethanol.

The rates of diffusion of PAPP and ethanol from solutions of different concentrations of PAPP in ethanolic phosphate buffer show very little variation (Table IX, Set C and Table XI). This demonstrates that the rates of diffusion of PAPP and ethanol are independent of each other.

The data from the quasi-steady state diffusion were treated specifically (Eqs. 31 and 32) to show the dependence of the apparent diffusion constants on the partition coefficients for PAPP between membrane and solutions on its two sides. The values of $(D'K_{p2}V_1 +$

$D'K_{p1}V_2$) (Table X) where D' is the intrinsic diffusion constant, K_{p1} and K_{p2} are the partition coefficients and V_1 and V_2 are the volumes of the solutions on two sides of the membrane, were obtained from the graphical analysis of the data and also calculated from the known values of the apparent diffusion constants $D'K_p$ for comparable conditions obtained from separate experiments (Table X, set A). In all the cases (Table X, sets B, C, D and E), the two sets of value are quite close to each other. It is apparent from the results (Table X) that partition coefficients on either side of the membrane form an integral part of the apparent diffusion constants. This observation together with the fact that the rates of diffusion of ethanol and PAPP are independent of each other (Table XI) indicate that the intrinsic diffusion constant of PAPP in Silastic membrane is not significantly dependent on the ethanol concentration on either side of the membrane.

It was noted previously that the partition coefficient is a ratio of the solubilities (100) in two media. In the case of diffusion of PAPP through Silastic membrane in the presence of ethanol, the premise of constancy of solubility in the membrane is warranted since only one compound is involved. Consequently the plot of the apparent diffusion constants of PAPP from ethanolic phosphate buffer through Silastic membrane versus the reciprocal of the solubilities of PAPP in these solutions (Table V) should be linear according to Eq. 39. This was found to be true as seen from linearity of the plot in Fig. 24. The regression analysis of the plot in Fig. 24 showed that at the 5% level of significance the intercept is not significantly different from zero.

Temperature Dependence of Diffusion in Silastic Membrane

The temperature dependence of diffusion in polymeric films may be expressed by

$$D = D_o \, e^{-\Delta Ea/RT} \qquad \text{(Eq. 3)}$$

where ΔEa is the apparent activation energy of diffusion. Barrer and Chio (98) have reported that the activation energy of diffusion of inert gases through silicone membrane is about 4 Kcal./mole.

The activation energy of diffusion in solution is theoretically about one-third of the energy of vaporization (101) and is in the range of 3-5 Kcal./mole. in many liquids. These calculations are based on the assumption that the diffusing molecules are large compared to the molecules of the medium into which they are diffusing and that the movement of the solvent molecules determines the rate of diffusion of the solute (102). It has also been pointed out that large diffusion constants have small temperature coefficients and conversely "more slowly diffusing substances have to form relatively large holes for the activated state; the activation energy and hence the temperature coefficient of diffusion are consequently large" (102).

In the diffusion of substances through polymers, the diffusing molecules are small compared to the molecules of the polymer. The polymer molecules are also rigidly fixed in position with respect to one another necessitating the diffusing species to move on its own. This should demand higher activation energies than the 3-5 Kcal./mole. postulated for diffusion in liquid media. However the results for inert gases and hydrocarbons (98, 99) demonstrate that the silicone rubbers may be considered to be liquidlike elastomers with great flexibility of atoms in an individual chain.

The effect of temperature on the rate of diffusion of 4'-aminopropiophenone through Silastic membrane is shown in Fig. 9. The apparent activation energies of diffusion ΔEa were calculated (Eq. 29) from the plots of the logarithm of the apparent diffusion constants versus the reciprocal of the absolute temperature for aminoalkylphenones (Fig. 10) and for barbituric acid derivatives (Fig. 17). The ΔEa values reported (Table IV and XI) vary within the small range of 4.9 to 7.5 Kcal./mole. except for mephobarbital and thiamylal.

The values of the apparent diffusion constants for aminoalkylphenones and barbituric acid derivatives are smaller than those reported (98, 99) for inert gases and the hydrocarbons. Consequently the apparent activation energies were higher as had been anticipated.

The apparent diffusion constant D, is a product of intrinsic diffusion constant D' in the membrane and the partition coefficient, K_p (Eq. 37). Since K_p is the ratio (Eq. 38) of the solubilities of the compound in the membrane S_m and the solvent for the drug solution S_a, Eq. 3 may be rewritten as

$$\log D = \log D'K_p = \log D'S_m/S_a = \log D_0 - \Delta Ea/2.303\ RT \qquad \text{(Eq. 40)}$$

If
$$\log S_m = \log S_{m0} - \Delta H_m/2.303\ RT \qquad \text{(Eq. 41)}$$

$$\log S_a = \log S_{a0} - \Delta H_a/2.303\ RT \qquad \text{(Eq. 42)}$$

and
$$\log D' = \log D'_0 - \Delta E_{D'}/2.303\ RT \qquad \text{(Eq. 43)}$$

then
$$\log D'S_m/S_a = \log S_{m0}D'_0/S_{a0} - [\Delta E_{D'} + (\Delta H_m - \Delta H_a)]/2.303\ RT \qquad \text{(Eq. 44)}$$

where $\Delta E_{D'}$ is the true activation energy of diffusion inside the membrane and ΔH_m and ΔH_a are the heats of solution for the compound in the membrane and the solvent phase. S_{m0}, S_{a0} and D'_0 are the pre-exponential factors in the Arrhenius equation, Eq. 3. Thus the apparent activation energy of diffusion is the sum of the true activation energy of diffusion inside the membrane and the difference between the heats of solutions of the diffusing species in the membrane and the solvent phase.

Pharmaceutical Application

The diffusion of drugs through Silastic membrane in steady state conditions is of zero order (Figs. 7, 9, 14, 15 and 18) when the concentration of the drug in the solution on one side of the membrane is kept constantly high by use of large volume of the solution of high concentration or by using a saturated solution in presence of large quantity of undissolved drug. The zero order release of a drug from a dosage form at a predetermined rate to exactly compensate the loss of drug from the body is ideal for a sustained release formulation (103). The diffusion of drugs from saturated solutions in Silastic capsules was studied with this view in mind. The concentrations of the drugs inside the capsules were thus kept constant for a long period of time.

The apparent diffusion constants for the compounds from the capsules are given in Table XVII, together with those obtained from the steady state diffusion studies in the diffusion cells, for the purpose of comparison. The two sets of values are comparable to each other. But the apparent diffusion constants calculated for diffusion from Silastic capsules are significantly lower than those from the diffusion cells. This is due to the fact that the area available for diffusion in Silastic capsules was calculated from geometrical considerations and the air entrapped in the capsules reduced this available area. Also the thickness of the part of the membrane changed to an unknown value because of the spread of the glue used for sealing the holes in the capsules. The two sets of values of apparent diffusion constants were, therefore, normalized with respect to the apparent diffusion constant of barbital in each set. The close agreement between these two sets of normalized values demonstrate that the apparent diffusion constants from Silastic capsules differed from those obtained with diffusion cells, by a constant factor.

The apparent diffusion constants of dextromethorphan and progesterone (Table XV, XVI and XVII) for diffusion from saturated solutions in non-aqueous solvents are much lower than those from saturated solutions in aqueous solvents. However because of the higher solubilities of the drugs in the non-aqueous solvents, higher concentrations are permissible and thus from these solvents the rates of diffusion of these drugs are greater than those from aqueous solvents (Figs. 19 and 20).

The specific rates of diffusion and apparent diffusion constants of dextromethorphan from mineral oil were higher than those from peanut oil (Table XV and XVII). This was expected as dextromethorphan is more soluble in peanut oil than in mineral oil and consequently the coefficient of partition from peanut oil to the membrane would be lower than that from mineral oil to the membrane. However the rate of diffusion is higher from saturated solution in peanut oil than that from saturated solution in mineral oil due to the higher concentration of drug attainable in the peanut oil. Thus the choice of a solvent to obtain a particular rate of diffusion from saturated solutions may be made on the basis of the solubility of the drug in a series of solvents.

Control and Prediction of Diffusion of Drugs through Silastic Membrane

It has been shown conclusively that the diffusion of drugs through Silastic membranes conform to Fick's law of diffusion. The apparent activation energy for diffusion has been shown to vary within a narrow range of 4.9 to 7.5 Kcal./mole. for most drugs studied.

If the diffusivity of a drug through Silastic membrane is obtained experimentally at one temperature, the apparent diffusion constants and the rates of diffusion at any other temperature can be predicted from Eqs. 4 and 29

$$dA/dt = DS\ dC/dx \qquad \text{(Eq. 4)}$$

$$\log D = \log D_0 - \Delta Ea/2.303\ RT \qquad \text{(Eq. 29)}$$

using a mean value of 5.7 Kcal./mole. for the term ΔEa, the apparent activation energy of diffusion. The optimum area S, and the thickness X of the membrane to obtain a pre-determined rate of diffusion may be calculated from Fick's law (Eq. 4) which reduces to

$$dA/dt = D\ S\ C/X \qquad \text{(Eq. 45)}$$

for a concentration C on the diffusing side of the membrane and when the concentration of the diffusing species is negligible on the desorbing side of the membrane.

The apparent diffusion constant has been shown to be a linear function of the partition coefficient or the ratio of the solubilities

$$D = D'K_p = D'S_m/S_a \qquad \text{(Eq. 39)}$$

where K_p is the partition coefficient and S_m and S_a are the solubilities of a compound in the membrane material and aqueous solvents respectively.

The diffusivity of compounds belonging to a homologous series can be predicted reasonably from the experimental value for diffusivity of a compound belonging to the series, and the partition coefficients and/or solubilities of these compounds. The linear relationship between the solubility and the diffusivity may be used to choose the best solvent to obtain a pre-determined rate of diffusion of a drug by studying the solubility of the drug in several solvents as in the case of 4'-aminopropiophenone in ethanolic phosphate buffers or dextromethorphan in peanut oil and mineral oil.

Thus the area and the thickness of the membrane and the solvent for the drug may be used to control the rate of diffusion. The Fick's law of diffusion, the apparent activation energy of diffusion and the knowledge of partition coefficients and/or solubility of drugs may be used for predicting the rates of diffusion of homologous series of drugs from the experimental value obtained for one of the members of the series.

SUMMARY AND CONCLUSIONS

1. Nine polymeric films were screened for their permeability to aminoalkylphenones, sulfonamides, steroids, barbituric acid derivatives, and other drugs. Silastic membrane was found to be permeable to many drugs in measurable quantities.

2. Silastic membrane was shown to be impermeable to HCl and phosphate buffer salts.

3. The rate of diffusion of 4'-aminopropiophenone through Silastic membrane was independent of ionic strength, and minor changes in the hydrostatic pressure.

4. The effect of concentration of drug solutions and thickness of Silastic membrane on the rate of diffusion of 4'-aminopropiophenone was studied by steady state diffusion technique. The zero order transport of the drug through the membrane conformed to Fick's law of diffusion

$$dA/dt = D\ S\ dC/dx \qquad \text{(Eq. 4)}$$

where D is the apparent diffusion constant, A is the amount transported in time t across a membrane of surface area S and with a concentration gradient of dC/dx.

5. The apparent diffusion constants D and the specific rates of diffusion [(dA/dt)/(concentration of diffusing drug)] through Silastic membranes were calculated for aminoalkylphenones, barbituric

acid derivatives, phenylalkylamines, dextromethorphan and progesterone.

6. The effect of temperature on the rate of diffusion of barbituric acid derivatives and aminoalkylphenones through Silastic membrane were studied and the activation energy of diffusion was observed to vary between 4.9 and 7.5 Kcal./mole. for these compounds except thiamylal (21.78) and mephobarbital.(15.22).

7. The effect of pH on the rate of diffusion of barbital, pentobarbital and 4'-aminopropiophenone through Silastic membrane was studied. The rate of diffusion was shown to be directly proportional to the concentration of the uncharged species. The pK_a values of these compounds calculated from the plot of apparent diffusion constants versus the pH of the solutions were observed to be the same as those obtained by other methods.

8. The apparent diffusion constants in Silastic membranes were found to be independent of the molecular weights of the diffusing species.

9. The transport of a drug across Silastic membrane was postulated to be due to partitioning of the drug from its solution into the membrane, its transport across the membrane and then repartitioning into the solution on other side of the membrane. This postulated mechanism was substantiated by quasi-steady state diffusion studies of 4'-aminopropiophenone from phosphate buffer solutions containing varying concentrations of ethanol into ethanolic phosphate buffer solutions. The intrinsic diffusion constant of 4'-aminopropiophenone in the membrane was independent of the composition of the solutions, since the data could be fitted to the equations derived on the assumption of constancy of intrinsic diffusion constant.

10. The apparent diffusion constants, D, of barbituric acid derivatives and aminoalkylphenones in Silastic membranes were shown to be lineraly related to their partition coefficients between aqueous solutions and chloroform. This was shown to be in accordance with the equation

$$D = D'K_p \tag{Eq. 37}$$

where D' is the intrinsic diffusion constant of a drug inside the Silastic membrane and K_p is the partition coefficient of the drug between the membrane and the drug solution.

11. The apparent diffusion constants in Silastic membranes were shown to be linearly related to the reciprocal of the solubilities of barbituric acid derivatives in acetate buffer and 4'-aminopropiophenone in phosphate buffer containing varying concentrations of ethanol. This was shown to be in accordance with equation

$$D = D'S_m/S_a \tag{Eq. 39}$$

where S_m and S_a are the solubilities of a drug in the membrane and the solvent for the drug solution.

12. The diffusion of dextromethorphan, pentobarbital, phenobarbital, barbital, and 4'-aminopropiophenone from saturated solutions in Silastic capsules was studied to investigate the feasibility of using Silastic membranes as encapsulating material for drugs. The rate of diffusion of dextromethorphan from peanut oil was greater than that from mineral oil because of the high concentration of the drug attainable in peanut oil. It was shown that

the rates of diffusion of a drug through Silastic membrane could be controlled by choice of a solvent for the drug solution. If a method of sealing the Silastic capsules, better than using a glue, is available, Silastic membranes can be used to encapsulate a drug solution to obtain its zero order release.

13. The area and the thickness of Silastic membranes and solvents for the drug solutions can be chosen to control the rate of diffusion of the drugs through Silastic membranes.

14. The apparent diffusion constants for diffusion of drugs through Silastic membranes can be estimated from the knowledge of partition coefficients and/or solubility of drugs belonging to a homologous series and the experimental apparent diffusion constant of one of the drugs from the series.

A. Tables

TABLE I

WAVELENGTHS OF MEASURED ABSORBANCES, MOLAR ABSORPTIVITIES AND pK_a VALUES OF COMPOUNDS.

Compounds	pK_a		Wavelength mμ	Molar Absorptivity
	Measured	Literature value (104)		
Amobarbital	7.40		238	5850
Barbital	7.45	7.91	238	8300
Butabarbital			238	10410
Cyclobarbital	7.27	7.50	238	8700
Diallyl barbituric acid	7.30	7.79	238	5990
Mephobarbital	7.45		238	6050
Metharbital	7.90		238	7700
Pentobarbital	7.65	8.11	238	8900
Phenobarbital	7.40	7.41	238	6800
Secobarbital	7.45	8.08	238	7700
Thiamylal	6.80		304	21000
Thiopental	7.12		304	13240
Dextromethorphan	8.25		277	3002
4'-aminopropiophenone	2.42		307	16016
4'-aminoacetophenone			312	13700
3'-aminoacetophenone			327	1840
α-methyl phenethylamine	9.07		520	
α-ethyl phenethylamine	9.30		520	
2-amino-4-methyl-4-phenylpentane	9.42		520	
3-amino-1-phenylbutane	9.30		520	
1-methyl-5-phenylpentylamine	9.50		520	
Progesterone			248	16470
Cortisone			238	16000
Hydrocortisone			242	16200
Prednisolone			242	15200
Sulfadiazine			255	5370
Sulfathiazole				
Sulfisoxazole				
Sulfabenzamide			255	4480

TABLE II

DIFFUSION OF 4'-AMINOPROPIOPHENONE FROM SATURATED SOLUTION (2.36×10^{-3} M) IN pH 6.5 PHOSPHATE BUFFER THROUGH 3 MIL SILASTIC MEMBRANE INTO 200 ML. OF 0.12 N HCl AT 37.3°.

Date	Time	Time Since Zero Hrs.	Temperature °C	Absorbance at 307 mμ[a] 1	2	3	4	5
7/16	10.00	0	37.30	0.007	0.004	0.008	0.014	0.006
	11.00	1.00	37.30	0.134	0.141	0.116	0.121	0.112
	12.00	2.00	37.30	0.234	0.224	0.232	0.207	0.209
	13.00	3.00	37.30	0.357	0.319	0.340	0.287	0.319
	14.00	4.00	37.50	0.478	0.428	0.460	0.395	0.433
	15.00	5.00	37.50	0.560	0.515	0.532	0.470	0.505
	16.00	6.00	37.30	0.663	0.602	0.653	0.559	0.612
	18.00	8.00	37.30	0.886	0.815	0.875	0.722	0.825
	Volume in the cell in ml.			21.0	22.0	23.0	23.0	22.0
	pH of cell solution			6.55	6.55	6.50	6.50	6.55
	Volume of solution in beaker in ml.			180	184	184	184	184
	pH of solution in the beaker			1.00	1.00	1.00	1.00	1.00

[a] The sample solutions were diluted 1:5 with pH 6.5 phosphate buffer before measurement of absorbances.

TABLE III

SOLUBILITIES[a], PARTITION COEFFICIENTS[b], AND APPARENT DIFFUSION CONSTANTS[c] OF BARBITURIC ACID DERIVATIVES AT 25.0°.

Compound	Solubility[a] 10^3 $\underline{M}$	Partition Coefficient[b] Experimental	Lt. Value (105)	1/Solubility $10^{-2}/\underline{M}$	Apparent Diffusion[c] Constant 10^{11}cm. /sec.
Amobarbital	3.222	19.85		3.103	5.38
Barbital	47.88	0.796	0.7	0.209	0.22
Butabarbital	7.98	9.98		1.253	2.40
Cyclobarbital	17.47	1.36	13.9	0.572	1.08
Diallybarbituric acid	13.73	3.00		0.728	1.26
Mephobarbital	0.302	Very High		33.15	8.64
Metharbital	9.78	55.70		1.023	9.05
Pentobarbital	3.697	25.80	28.0	2.705	4.74
Phenobarbital	5.06	4.48	4.70	1.98	0.66
Secobarbital	7.38	50.54	50.7	1.36	8.95
Thiamylal	0.310	Very High		32.31	33.95
Thiopental	0.75	Very High		13.34	34.90

[a] Solubility in pH 4.7 acetate buffer.

[b] Concentration in chloroform/concentration in acetate buffer; both phases saturated with each other.

[c] Apparent diffusion constant calculated from Eq. 24, $A = DSt(C_2 - C_1)/X$ for diffusion through 3 mil Silastic membrane from pH 4.7 acetate buffer.

TABLE IV

PARTITION COEFFICIENTS[a], SOLUBILITIES[b], ACTIVATION ENERGIES OF DIFFUSION[c], AND APPARENT DIFFUSION CONSTANTS[d] OF AMINOALKYLPHENONES

Compound		4'-aminoacetophenone	3'-aminoacetophenone	4'-aminopropiophenone
Partition [a] coefficient at 25.0°		15.97	53.30	134.4
Solubility [b] at 37.5° $10^3 \underline{M}$		24.8	52.2	2.36
Apparent [d] diffusion constants 10^{10} cm.^{2}/sec.	25.0°	1.10	2.21	3.42
	37.5°	1.84	3.62	4.82
Activation [c] energy ΔE_a Kcal/mole.		7.55	7.49	4.90

[a] Concentration in chloroform/concentration in pH 6.8 phosphate buffer solution at 25.0°.

[b] Solubility in pH 6.8 phosphate buffer at 37.5°.

[c] Calculated from Eq. 29, $\log D = \log D_o - \Delta E_a/2.303\ RT$

[d] Apparent diffusion constants calculated from Eq. 24, $A = DSt(C_2 - C_1)/X$ for diffusion through 3 mil Silastic membrane from phosphate buffer into 0.12 $\underline{N}$ HCl.

TABLE V

SOLUBILITY[a], AND APPARENT DIFFUSION CONSTANTS[b] OF 4'-AMINOPROPIOPHENONE AS A FUNCTION OF ETHANOL CONCENTRATION AT 25.0°.

% Ethanol in Phosphate buffer	Solubility [a] 10^3 Moles/Liter	1/Solubility 10^{-1} Liter/Moles	Apparent Diffusion Constant [b] 10^{10} cm.^{2}/sec.
0	2.33	42.90	3.49
7.5	3.15	31.75	2.27
15.0	5.63	17.76	1.88
22.5	9.30	10.75	0.97
30.0	14.43	6.93	0.80
37.5	25.20	3.97	0.64

[a] Solubility in pH 6.8 phosphate buffer containing various percentages of ethanol interpolated from Fig. 6 showing solubility of PAPP as function of ethanol concentration.

[b] Apparent diffusion constants calculated from Eq. 24, $A = DSt(C_2 - C_1)/X$ for diffusion through 3 mil Silastic membrane from ethanolic phosphate buffer solutions into ethanolic HCl solutions.

TABLE VI

SPECIFIC RATES OF DIFFUSION[a] OF 4'-AMINOPROPIOPHENONE AS A FUNCTION OF MEMBRANE THICKNESS AT 24.90°.

Labelled thickness	mil	3	5	10	20
Measured thickness [b]	mil	2.96 ± 0.047	5.66 ± 0.0908	10.51 ± 0.0958	18.64 ± 0.0630
Coefficient of variation [c]	%	6.42	6.36	3.62	1.34
Mean thickness	10^3 cm.	7.52	14.38	26.70	47.35
1/thickness	10^{-1}cm.$^{-1}$	13.30	6.95	3.75	2.11
Slopes of concentration vs. time	$10^5$$\underline{M}$/hr.	1.436	0.749	0.406	0.250
Specific rates of diffusion [a]	10^8cm./sec.	5.06	2.64	1.43	0.88

[a] (Slope of concentration versus time plot) (volume)/(area) (concentration of diffusing solution).

[b] Mean thickness and 95% confidence limits.

[c] Standard deviation/mean.

TABLE VII

SPECIFIC RATES OF DIFFUSION[a], AND APPARENT DIFFUSION CONSTANTS[b] OF 4'-AMINOPROPIOPHENONE AS FUNCTION OF TEMPERATURE AND CONCENTRATION

Temperature °C	$10^5/°K$	Concentration 10^4M	Slope of Conc. vs. Time Plot 10^6M	Specific Rate of Diffusion[a] 10^3hr.$^{-1}$	Apparent Diffusion Constant[b] 10^{10}cm.^{2}/sec.
24.75	335.6	3.31	2.47	8.30	3.33
		7.21	5.59		
		9.48	7.74		
		11.37	9.12		
		13.99	11.23		
		16.45	13.30		
24.90	335.4	3.62	2.98	8.70	3.49
		9.80	8.18		
		12.10	10.23		
		18.30	15.77		
30.40	329.5	3.73	3.68	9.00	3.62
		9.21	9.68		
		10.93	10.20		
		16.71	15.30		
31.25	328.4	3.65	3.93	10.10	4.06
		9.33	9.43		
		13.74	14.10		
		18.24	21.20		
33.60	325.90	3.13	3.75	11.0	4.42
		9.96	11.20		
		14.67	16.50		
		19.11	21.20		
37.50	321.8	3.62	4.18	12.00	4.82
		9.37	10.40		
		13.49	16.70		
		17.73	21.20		
41.0	318.2	3.64	5.87	14.0	5.62
		9.68	14.40		
		13.99	20.00		
		18.79	27.20		

[a] Rates of diffusion through 3 mil Silastic membrane from pH 6.5 phosphate buffer into 0.12 N HCl calculated as slopes obtained by plotting the slopes of concentration of diffused material versus time against concentration of diffusing solution.

[b] Apparent diffusion constants calculated from Eq. 24, $A = DSt(C_2 - C_1)/X$

TABLE VIII

APPARENT DIFFUSION CONSTANTS[a] OF 4'-AMINOPROPIOPHENONE AS A FUNCTION OF pH AT 25.0°.

pH	Medium	Concentration of PAPP 10^3 M	Specific[b] Rate of Diffusion 10^3 hr.$^{-1}$	Apparent[a] Diffusion Constant 10^{10}cm. /sec.
1.30	HCl	1.685	0.630	0.208
2.00	HCl	1.655	3.056	1.007
2.45	HCl	1.639	5.714	1.882
3.48	Acetate buffer	1.592	8.236	2.711
4.38	Acetate buffer	1.59	9.888	3.25
5.47	Acetate buffer	1.670	10.97	3.61
6.70	Phosphate buffer	3.310	11.10	3.66

[a] Calculated from Eq. 24, $A = DSt(C_2 - C_1)/X$ for diffusion through 2.43 mil thick Silastic membrane.

[b] Slopes of concentration versus time plots/concentrations in solution.

TABLE IX

APPARENT DIFFUSION CONSTANTS[a], AND SPECIFIC RATES OF DIFFUSION[b] OF 4'-AMINOPROPIOPHENONE AS A FUNCTION OF ETHANOL CONCENTRATION AT 24.60°.

	% Ethanol in		Concentration of PAPP 10^3 M	Specific Rate of Diffusion 10^3 hr.$^{-1}$ [b]	Apparent Diffusion Constant 10^{10}cm.^{2}/sec. [a]
	Phosphate Buffer	0.12 N HCl			
	7.5	7.5	1.402	5.66	2.27
	15.0	15.0	1.445	4.68	1.88
A	22.5	22.5	1.655	2.42	0.97
	30.0	30.0	1.561	2.00	0.80
	37.5	37.5	1.445	1.60	0.64
	45.0	45.0	1.467	1.15	0.46
	0	0	1.31	8.78	3.53
	0	10	1.31	10.0	4.02
B	0	20	1.31	9.77	3.92
	0	30	1.31	9.77	3.92
	0	40	1.31	9.77	3.92
	0	50	1.31	10.2	4.10
	18	0	1.87	4.57	1.84
	18	0	2.43	4.81	1.93
C	18	0	2.78	4.87	1.96
	18	0	3.28	4.61	1.85
	In Water	0.1 N HCl			
	0	0	2.40	8.01	3.22
D	10	10	2.98	6.81	2.74
	30	30	9.13	2.502	1.01
	50	50	36.2	0.812	0.33

[a] Calculated from Eq. 24, $A = DSt(C_2 - C_1)/X$ for diffusion through 3 mil Silastic membrane.

[b] Slopes of concentration versus time/concentration in solution.

TABLE X

CONSTANTS OF QUASI-STEADY STATE DIFFUSION OF 4'-AMINOPROPIOPHENONE THROUGH SILASTIC MEMBRANE AS A FUNCTION OF ETHANOL CONCENTRATION AT 25.25°.

Set	Concentration of ethanol in %		Values of $D'K_p$ 10^{10} cm.2/sec.		$D'K_{p2}V_1 + D'K_{p1}V_2$ 10^{10}(cm.^{2}/sec.)(cm.^{3})	
	cell	beaker	$D'K_{p2}$	$D'K_{p1}$	Obtained[c]	Calculated[d]
A[a]	0	0	2.405	2.405	1.48	1.49
	10	10	1.752	1.752	1.09	1.09
	20	20	1.237	1.237	0.77	0.77
	30	30	1.849	0.849	0.53	0.53
B[b]	0	10	2.405	1.752	1.15	1.16
	0	20	2.405	1.237	1.00	0.91
	0	30	2.405	0.849	0.81	0.71
C[b]	10	0	1.752	2.405	1.40	1.41
	10	20	1.752	1.237	0.93	0.83
	10	30	1.752	0.849	0.70	0.63
D[b]	20	0	1.237	2.405	1.45	1.35
	20	10	1.237	1.752	1.00	1.02
	20	30	1.237	0.849	0.60	0.57
E[b]	30	0	0.849	2.405	1.20	1.30
	30	10	0.849	1.752	0.91	0.98
	30	20	0.849	1.237	0.72	0.72

[a] In this case $D'K_{p1} = D'K_{p2} = D$, which are apparent diffusion constants calculated from Eq. 32

$$\ln C_0V_2/ (C_0V_2 - C_1(V_1 + V_2)) = DSt(V_1 + V_2)/XV_1V_2$$

[b] In this case $D'K_{p1}$ and $D'K_{p2}$ are the values for comparable compositions in Set A.

[c] Calculated from the slopes obtained from the plot of the logarithmic term constructed from the appropriate values of $D'K_{p1}$, $D'K_{p2}$, V_1 and V_2 and the known experimental values versus time in Eq. 31

$$\ln[D'K_{p2}C_0V_2/(D'K_{p2}C_0V_2 - C_1(D'K_{p2}V_1 + D'K_{p1}V_2))] = (D'K_{p2}V_1 + D'K_{p1}V_2)St/XV_1V_2$$

[d] Calculated from known values of $D'K_{p1}$, $D'K_{p2}$, V_1 and V_2.

TABLE XI

SPECIFIC RATES OF DIFFUSION OF ETHANOL[a] AS A FUNCTION OF 4'-AMINOPROPIOPHENONE CONCENTRATION AT 24.60°.

Concentration of Ethanol %	Concentration of PAPP 10^3 M	Slope of % Ethanol versus Time %/hr.	Specific rate[a] of diffusion 10^3 hr.$^{-1}$
18	0	0.032	1.77
18	1.90	0.032	1.77
18	3.01	0.032	1.77
18	5.06	0.032	1.77
10	0	0.0143	1.43
20	0	0.0273	1.37
30	0	0.0453	1.51
40	0	0.0633	1.53
50	0	0.0777	1.56

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[a] Calculated for diffusion of ethanol through 3 mil Silastic membrane by dividing slope of the plot of the percent ethanol diffused versus time, by percentage of ethanol in solution.

TABLE XII

APPARENT ACTIVATION ENERGIES OF DIFFUSION[a], AND APPARENT DIFFUSION CONSTANTS[b] OF BARBITURIC ACID DERIVATIVES

Compound	Temperature °C	Concentration 10^3 M	Specific[c] Rate of Diffusion 10^4 hr.$^{-1}$	Apparent[b] Diffusion Constant 10^{11} cm^2/sec.	Temperature °C	Concentration 10^3 M	Specific[c] Rate of Diffusion 10^4 hr.$^{-1}$	Apparent[b] Diffusion Constant 10^{11} cm^2/sec.	Activation[a] Energy ΔE_a Kcal/mole
Amobarbital	24.65	3.11	13.41	5.38	37.0	3.35	20.16	8.10	6.07
Barbital	24.10	3.67	0.54	0.217	37.0	34.64	0.841	0.338	6.29
Butabarbital	24.65	1.96	5.98	2.40	37.2	2.181	9.87	3.96	7.32
Cyclobarbital	24.65	2.46	2.69	1.08	37.2	2.77	4.23	1.70	6.63
Diallyl barbituric acid	24.65	3.77	3.14	1.26	37.5	3.84	4.04	1.62	3.59
Mephobarbital	24.65	0.96	21.52	8.64	37.2	0.87	60.94	24.48	15.22
Metharbital	24.65	1.17	22.53	9.05	37.2	2.36	33.06	13.28	5.61
Pentobarbital	24.10	4.61	11.80	4.74	37.0	4.52	19.21	7.71	6.91
Phenobarbital	24.10	6.53	1.64	0.66	37.0	5.91	2.61	1.05	
Secobarbital	24.65	2.39	22.28	8.95	37.2	2.35	35.69	14.34	6.59
Thiamylal	24.65	0.25	83.59	33.59	37.2	0.38	370.80	148.95	21.78
Thiopental	24.10	0.80	216.33	86.90	37.0	0.42	342.32	137.51	6.51

[a] Calculated from Eq. 29, $\log D = \log D_o - \Delta Ea/2.303\ RT$.

[b] Calculated from Eq. 24, $A = DSt(C_2 - C_1)/X$ for diffusion from pH 4.7 acetate buffer through 3 mil thick Silastic membrane.

[c] Slopes of concentration versus time/concentration of drug in solution.

TABLE XIII

APPARENT DIFFUSION CONSTANTS[a] OF BARBITAL AND PENTOBARBITAL THROUGH SILASTIC MEMBRANE AT 37.3° AS A FUNCTION OF pH

Barbital		Pentobarbital	
pH	Apparent Diffusion Constant 10^{13} cm.^{2}/sec.	pH	Apparent Diffusion Constant 10^{13} cm.^{2}/sec.
4.70	33.80	4.60	7.71
6.65	26.08	6.99	7.54
7.30	21.67	7.57	5.58
7.60	15.01	7.90	4.05
8.12	8.83	8.18	3.12
9.15	5.02	8.65	1.53
9.75	2.95	9.05	0.50
10.55	0.65	9.53	0.57

[a] Calculated for Eq. 24, $A = DSt(C_2 - C_1)/X$

TABLE XIV

APPARENT DIFFUSION CONSTANTS[a], AND SPECIFIC RATES OF DIFFUSION[b] OF PHENYLALKYLAMINES THROUGH SILASTIC MEMBRANE AT 25.0° FROM BORATE BUFFER SOLUTIONS INTO 120 ML. OF pH 6.8 PHOSPHATE BUFFER

Compound	pK_a	pH	Total Concentration $10^3 \underline{M}$	Concentration of free base[c] $10^3 \underline{M}$	Specific Rates of Diffusion[b] 10^2 hr.$^{-1}$	Apparent Diffusion Constant[a] cm.^{2}/sec. 10^{10}
α-methylphenethylamine	9.07	8.93	3.18	1.55	2.84	6.84
3-amino-1-phenylbutane	9.30	9.40	2.47	1.647	5.00	12.05
1-methyl-5-phenylpentylamine	9.50	9.60	0.875	0.537	13.41	32.32
α-ethylphenethylamine	9.30	9.28	1.79	0.917	7.80	18.80
2-amino-4-methyl-4-phenylpentane	9.42	9.45	0.325	0.190	5.74	13.83

[a] Calculated from Eq. 24, $A = DSt(C_2 - C_1)/X$

[b] Slopes of concentration versus time/concentration of solution.

[c] Calculated from the equation $pH = pK_a + \log [base]/[salt]$.

TABLE XV

APPARENT DIFFUSION CONSTANTS[a], AND RATES OF DIFFUSION[b] OF. DEXTROMETHORPHAN FROM PEANUT OIL, MINERAL OIL AND pH 10.1 BORATE BUFFER THROUGH 3 MIL SILASTIC MEMBRANE INTO pH 6.8 PHOSPHATE BUFFER AT 37.5°.

Dextromethorphan Solution in	Peanut Oil (Subsaturated)	Peanut Oil (Saturated)	Mineral Oil (Saturated)	Borate Buffer (Saturated)
Concentration 10^2 M	8.97	32.90	1.35	0.0105
Rate of Diffusion[b] 10^4 M/hr.	0.6062	2.76	2.10	1.31
Volume of Phosphate Buffer ml.	200	120	120	20
Apparent Diffusion[a] Constant 10^{11} cm.^{2}/sec.	2.72	2.02	37.5	501.0

[a] Calculated from Eq. 24, $A = DSt(C_2 - C_1)/X$

[b] Slopes of concentration versus time.

TABLE XVI

APPARENT DIFFUSION CONSTANTS[a] OF PROGESTERONE FROM PEANUT OIL, AND pH 6.8 PHOSPHATE BUFFER THROUGH 3 MIL SILASTIC MEMBRANE INTO pH 6.8 PHOSPHATE BUFFER AT 37.5°.

Solution in	Peanut Oil	Phosphate Buffer (Saturated)
Concentration M	8.34×10^{-2}	5.98×10^{-5}
Volume of Phosphate Buffer ml.	200	120
Apparent Diffusion Constant 10^{12} cm.^{2}/sec.	0.377	629.7

[a] Calculated from Eq. 85

$\log (C_{eq.} - C_1/C_0) = \log (V_2/(V_1 + V_2)) - DSt[(V_1 + V_2)/(V_1V_2)]/2.303X$

TABLE XVII

APPARENT DIFFUSION CONSTANTS[a] AND RATES OF DIFFUSION[b] OF DRUGS FROM SILASTIC CAPSULES AT 37.5°.

Compound	Solution in	Specific Rates of Diffusion[b] 10^4 hr.$^{-1}$	Apparent Diffusion Constants[a] 10^{11} cm.^{2}/sec. Silastic capsules	Diffusion cell	Normalized Values[c] Silastic capsules	Diffusion cell
Barbital	Acetate buffer	2.18	0.170	0.338	1.00	1.00
Phenobarbital	Acetate buffer	9.55	0.745	1.05	4.382	3.11
Pentobarbital	Acetate buffer	4.89	3.81	7.71	22.41	22.81
4'-Aminopropiophenone	Phosphate buffer	29.8	38.9	48.2	251.24	142.60
Dextromethorphan	Borate buffer	19.7	154.0	501.0	905.88	1482.24
Dextromethorphan	Peanut oil	0.967	0.754	2.02	4.38	5.98
Dextromethorphan	Mineral oil	25.0	19.5	37.5	114.71	110.95

[a] Calculated from Eq. 24, $A = D\,S\,(C_2 - C_1)t/X$

[b] Slopes of concentration versus time/concentration in solution.

[c] Apparent diffusion constants/apparent diffusion constants of barbital in respective columns.

B. Figures

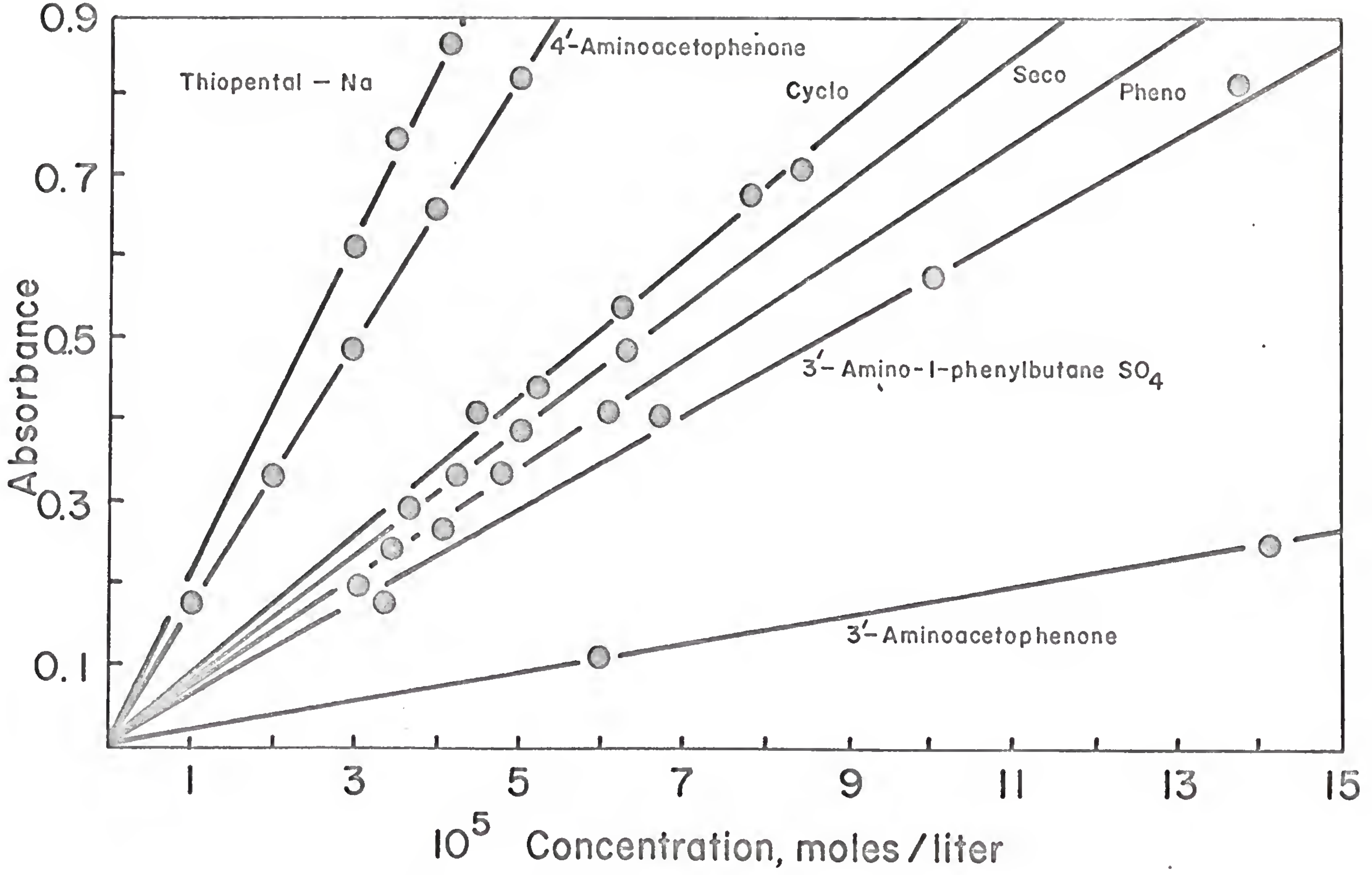
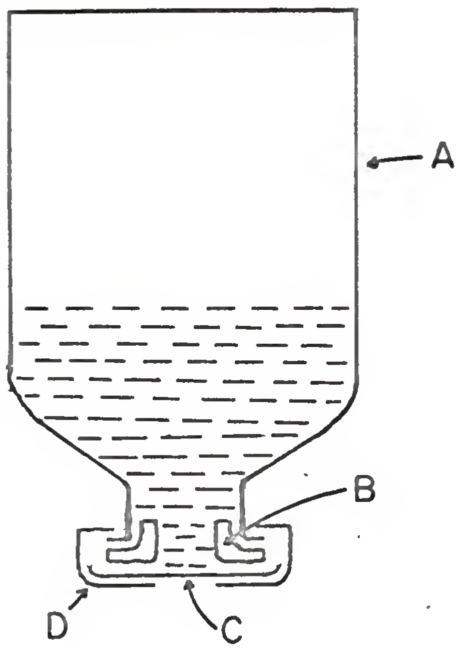


Fig. 1.—Typical calibration curves for spectrophotometric analyses of various drugs at their pertinent wavelengths.
(Cyclo - cyclobarbital, Seco - secobarbital, and Pheno - phenobarbital (238 mμ),; 3'-amino-1-phenylbutane SO_4 (520 mμ); 4'-aminopropiophenone (307 mμ); 3'-aminoacetophenone (312 mμ); thiopental-Na (304 mμ))



Glass Vial for Preliminary Diffusion Screening

A – 10 cc Serum Vial.
B – Rubber Stopper with hole.
C – Membrane.
D – Aluminum Cap.

Fig. 2.—Sketch of an assembled vial for screening polymeric films for their permeability to drugs.

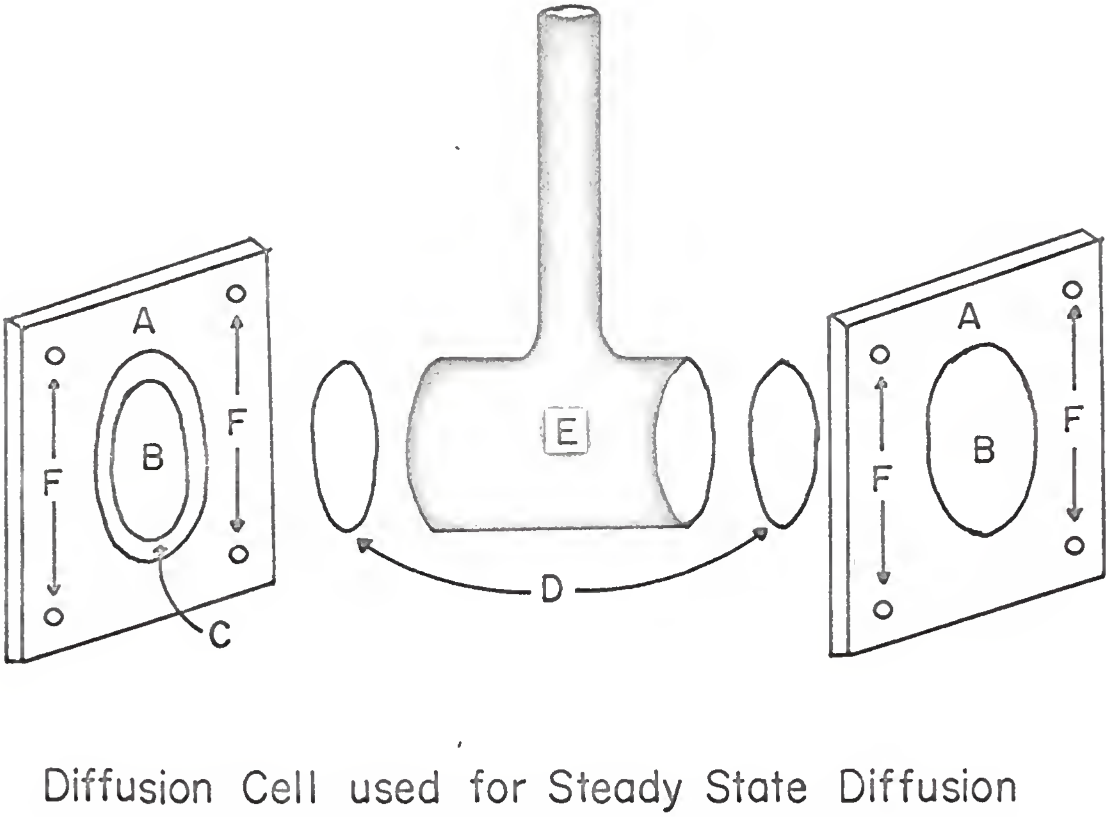


Fig. 3.—Sketch of diffusion cell used for steady state diffusion.

A - Stainless steel plates (2 1/2" x 2" x 1/8")
B - Hole in stainless steel plate (2.57 cm. in diameter)
C - Recessed border around hole B (0.43 cm. in width from the perimeter of the hole and recessed 2 mm. into the stainless steel plate)
D - Silicone rubber gaskets (2.57 cm. i.d.; 2.95 cm. o.d.; 0.16 cm. thick)
E - Glass T joint
    Horizontal glass cylinder (2.6 cm. in diameter, 3 cm. long)
    Vertical Stem (0.8 cm. in diameter and 11 cm. long)
F - Holes for stainless steel bolts

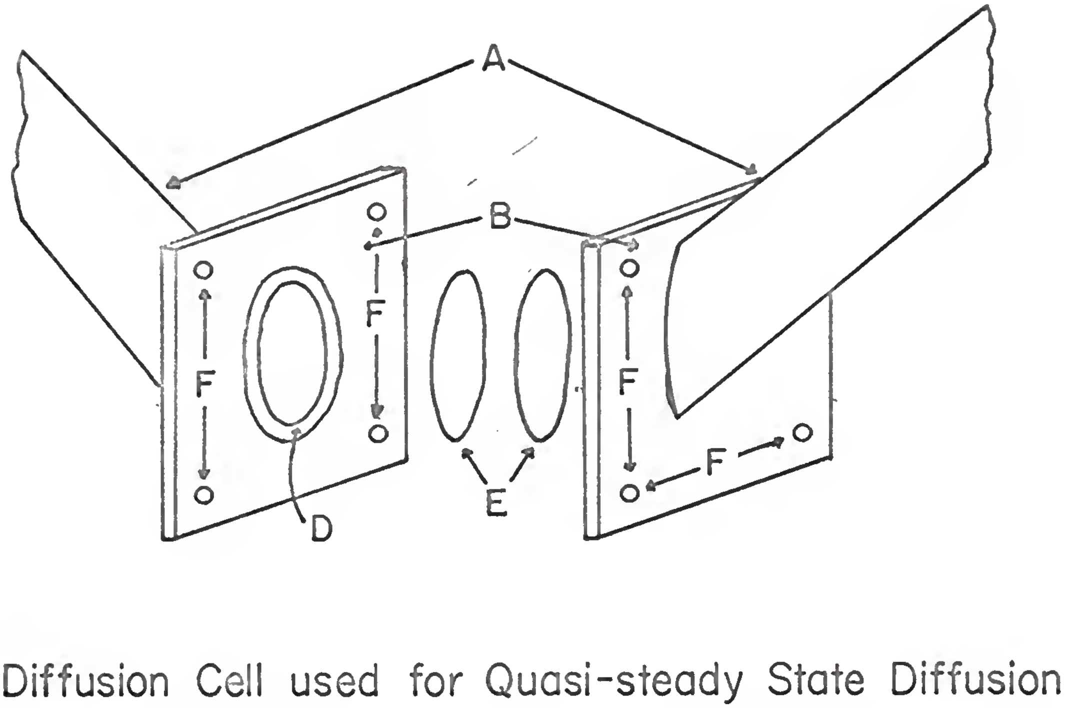
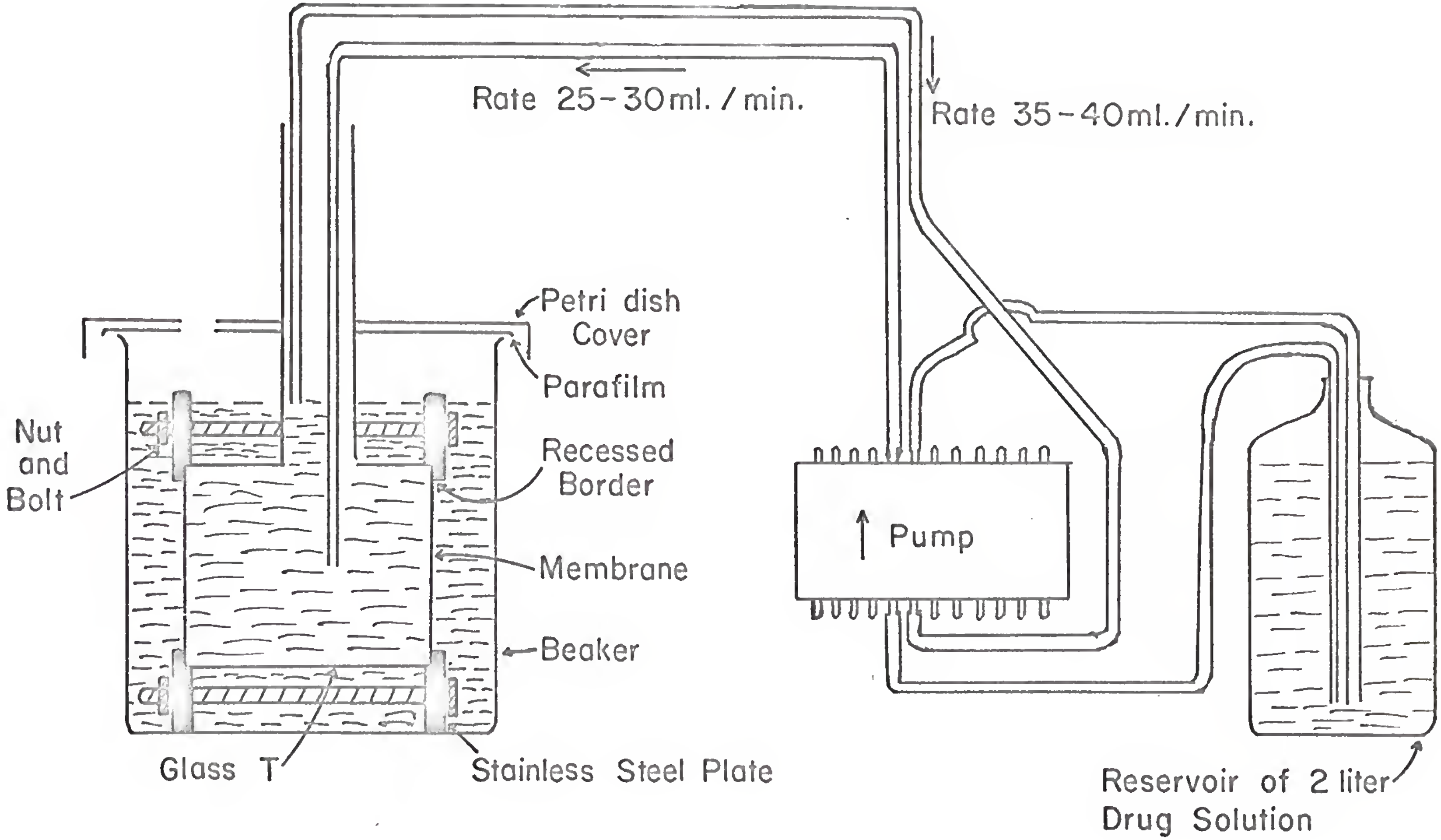


Fig. 4.—Sketch of diffusion cell used for quasi-steady state diffusion.

A - Stainless steel cylinders (1 1/2" in diameter, 7" long)
B - Stainless steel plates (2 1/2" x 2 1/2" x 1/8")
C - Hole in stainless steel plate (3.1 cm. in diameter)
D - Recessed border around hole C (0.8 cm. in width from perimeter of the hole and recessed 2 mm. into the stainless steel plate)
E - Silicone rubber gaskets (3.1 cm. i.d.; 3.8 cm. o.d.; 3 mm. thick)
F - Holes for stainless steel bolts



Schematic for Steady State Diffusion Assembly

Fig. 5.—Sketch of diffusion apparatus and pump assembly for steady state diffusion studies.

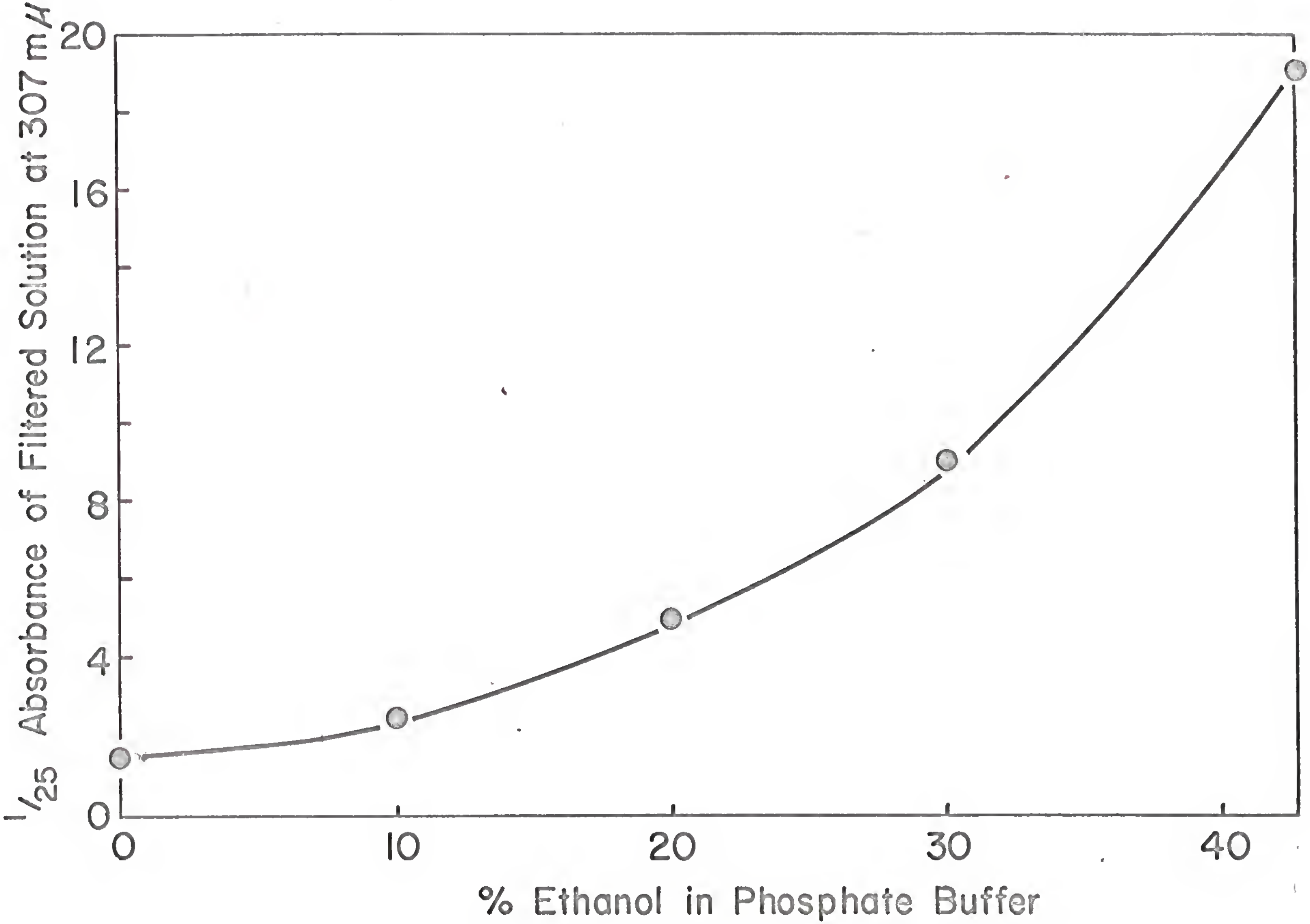


Fig. 6.—Solubility of 4'-aminopropiophenone in phosphate buffer containing various concentrations of ethanol at 25.0° plotted as absorbance of the filtered solutions at 307 mμ versus percentage of ethanol in phosphate buffer.

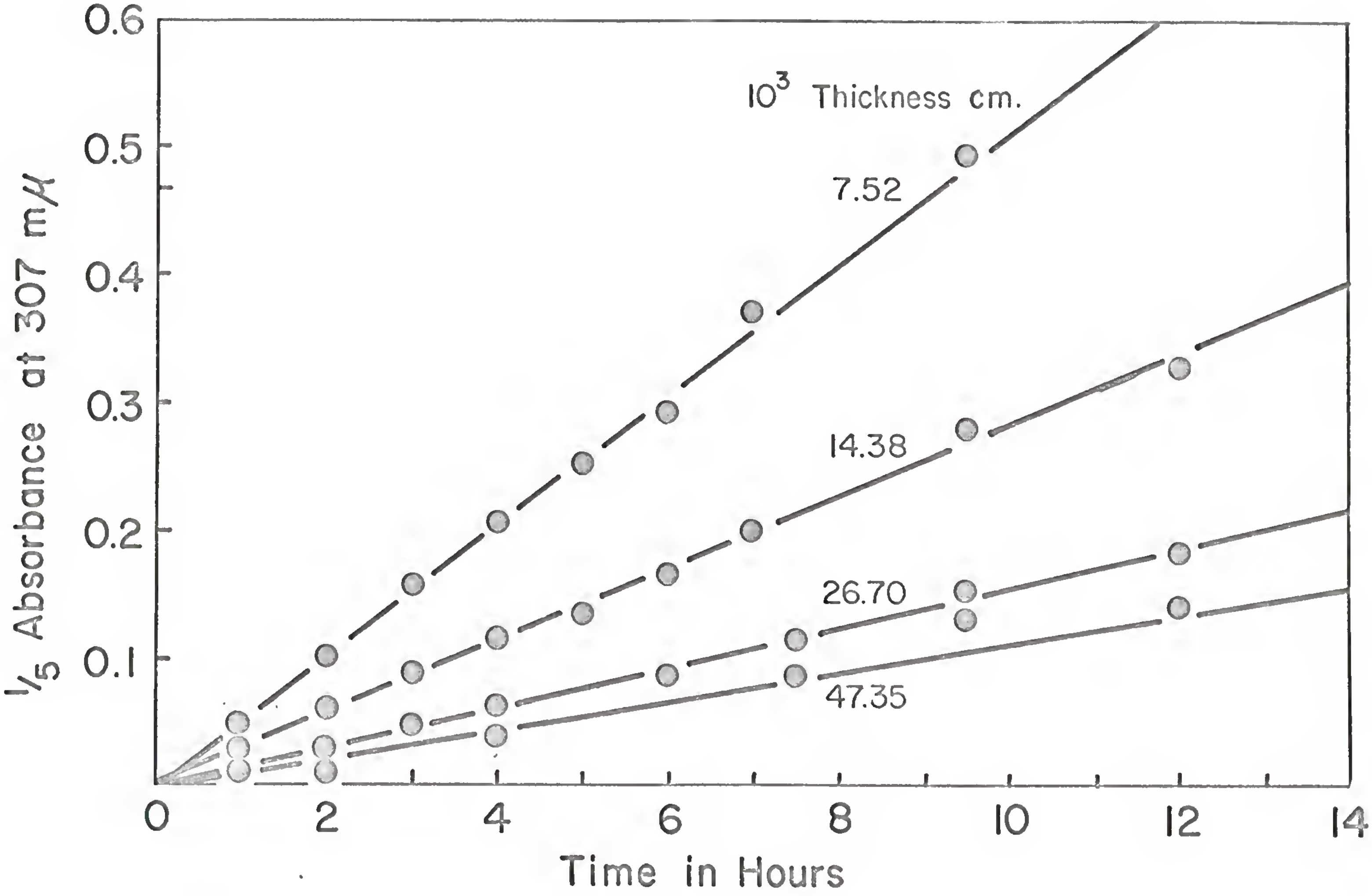


Fig. 7.—Diffusion of 4'-aminopropiophenone (1.52×10^{-3} M) from pH 6.8 phosphate buffer through Silastic membranes of different thicknesses at 24.90°. (The absorbance of the desorbant solution was measured as a function of time.)

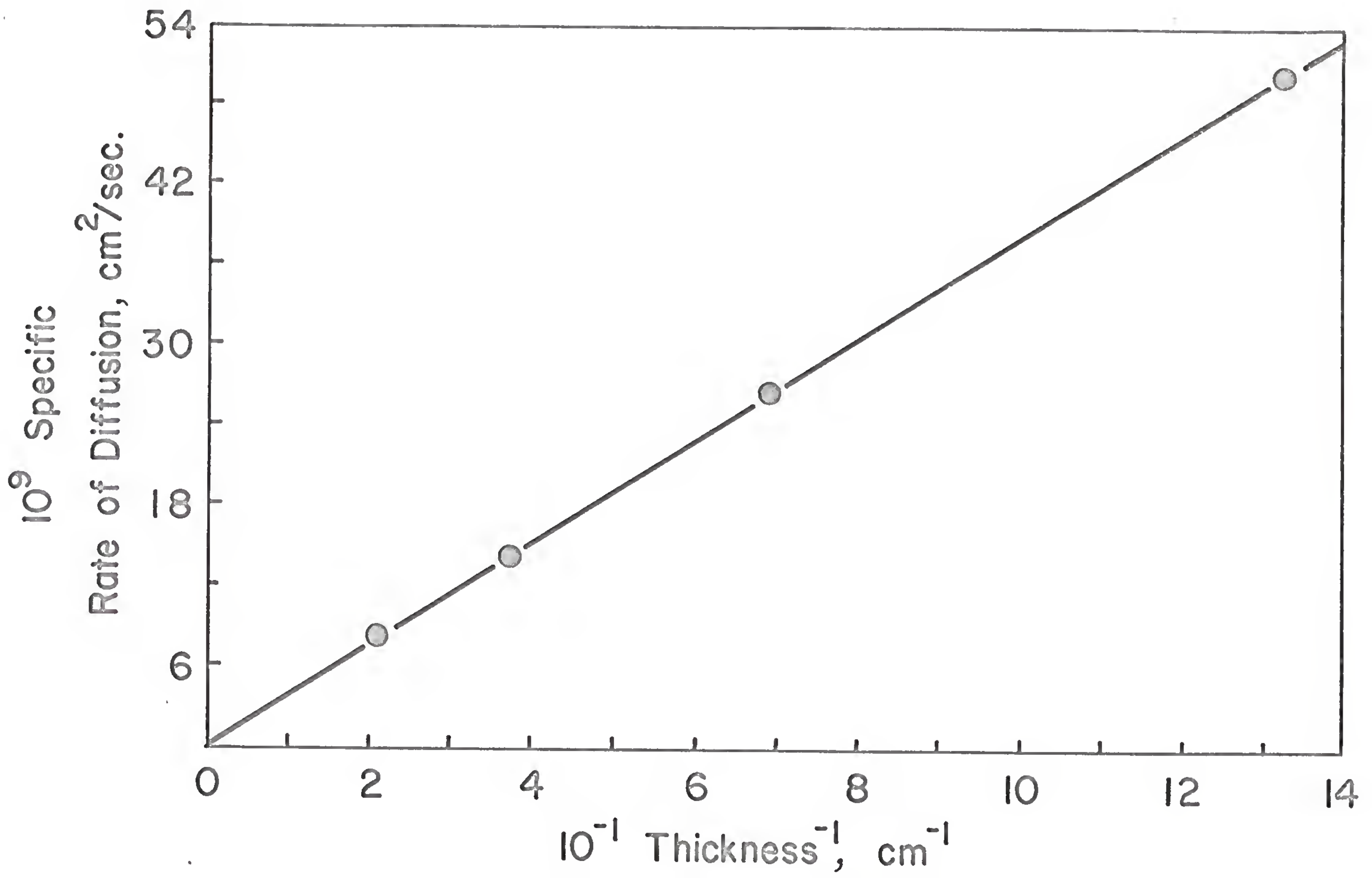


Fig. 8.—Effect of thickness of Silastic membrane on the specific rate of diffusion (rate of diffusion/concentration x area) of 4'-aminopropiophenone from phosphate buffer solutions at 24.90°.

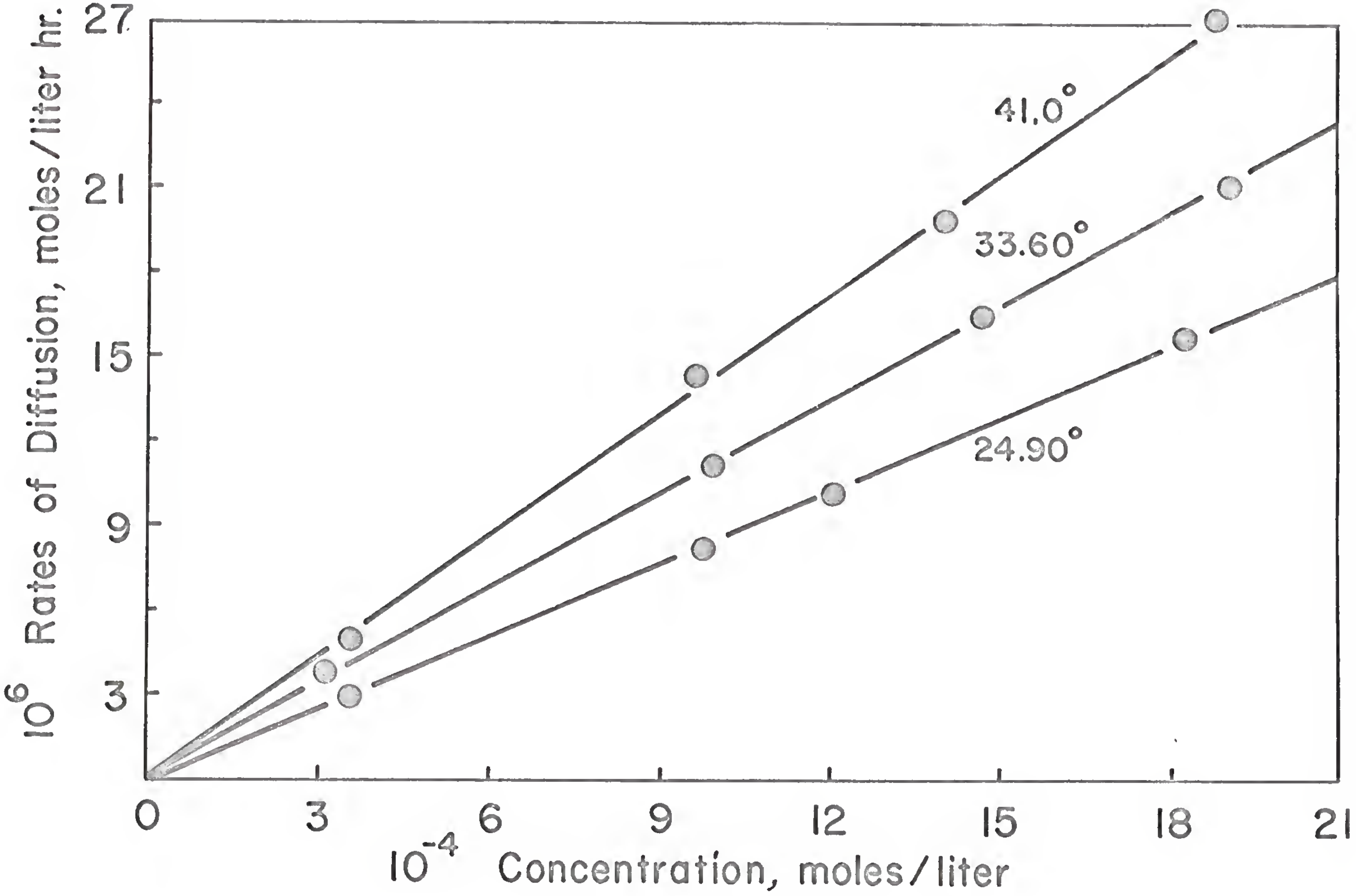


Fig. 9.—Effect of concentration of 4'-aminopropiophenone in phosphate buffer solution on the rate of diffusion of the drug through 3 mil Silastic membrane at 24.90°, 33.60°, and 41.0°.

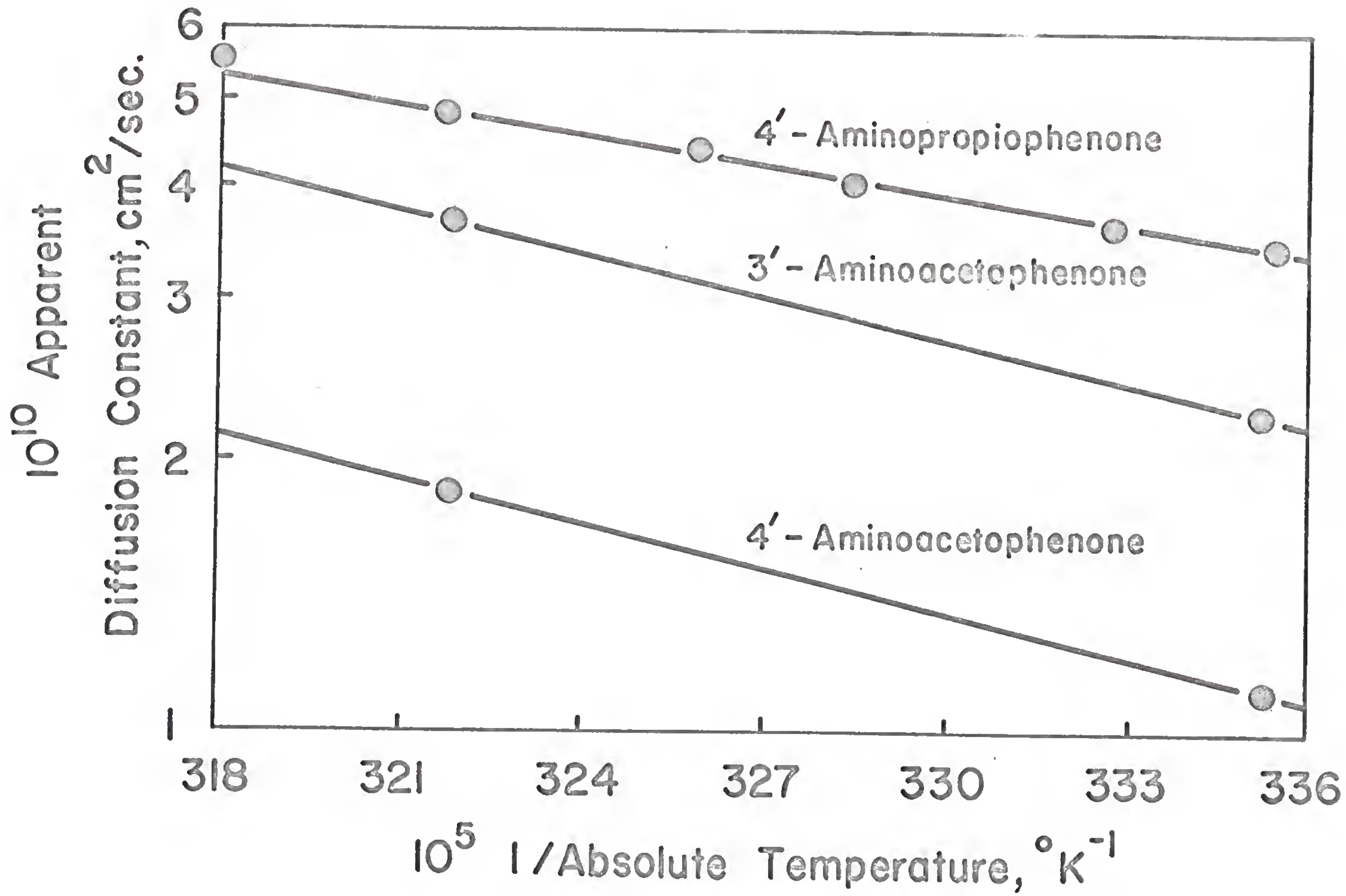


Fig. 10.—Arrhenius plot for the apparent diffusion constants of aminoalkylphenones through 3 mil Silastic membrane from phosphate buffer solutions.

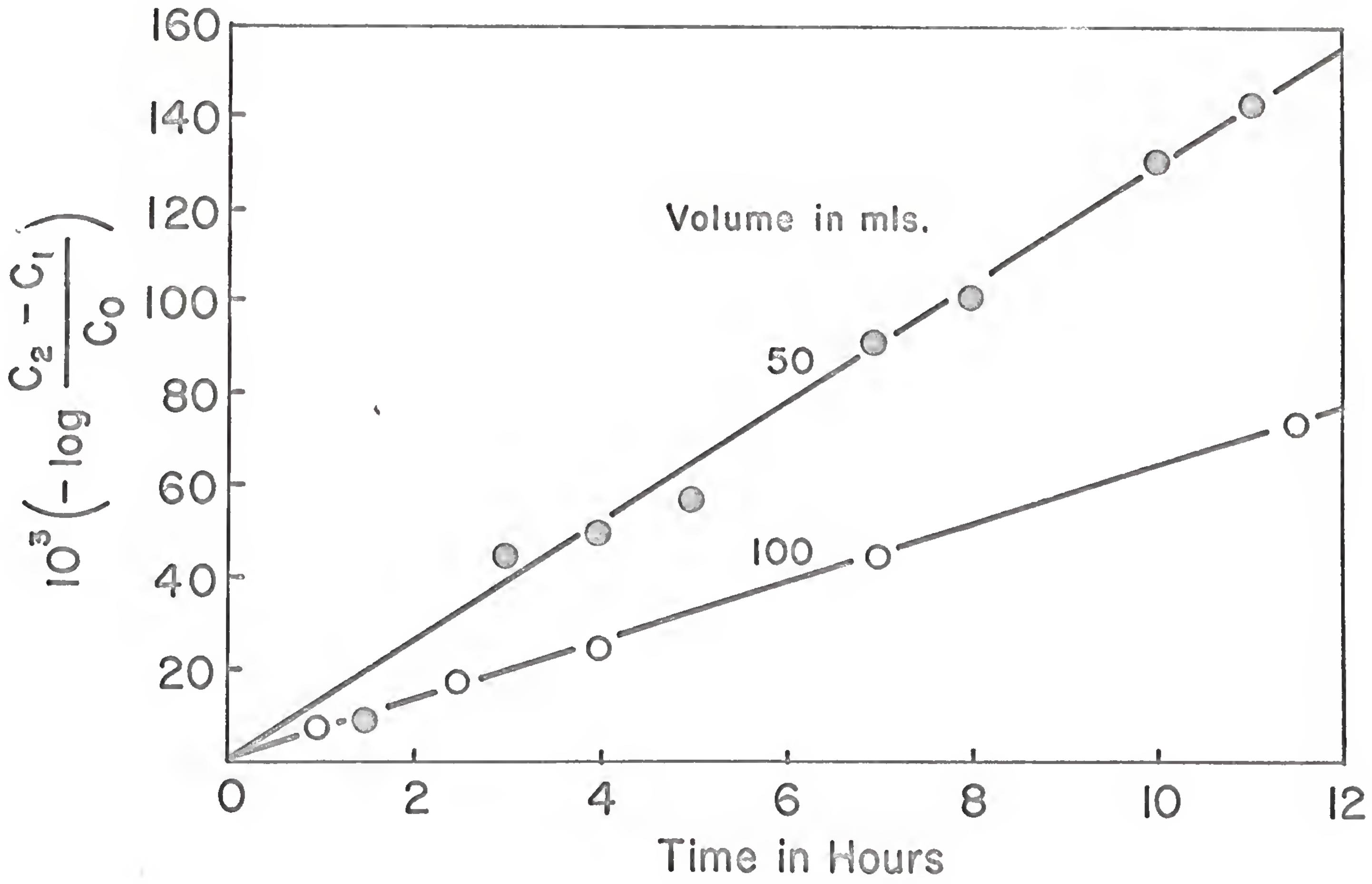


Fig. 11.—A plot of - log (C_2 - C_1/C_0) versus time for quasi-steady state diffusion of 4'-aminopropiophenone from phosphate buffer through 5 mil Silastic membrane at 25.0°. (C_2 and C_1 are the concentrations of the drug in equal volumes of 50 ml or 100 ml of phosphate buffer in the two arms of the diffusion cell and C_0 is the initial concentration of the drug in one arm.)

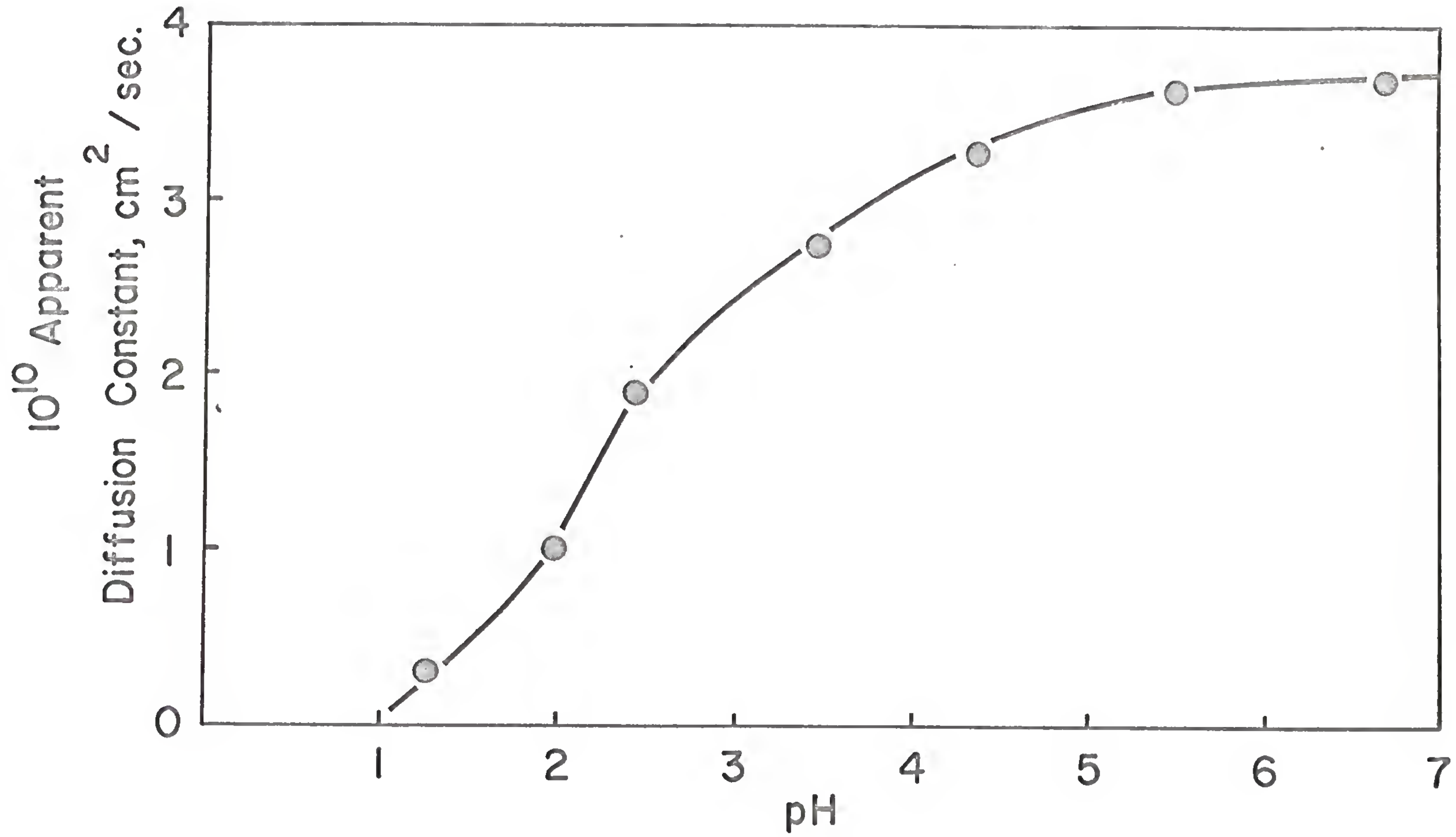


Fig. 12.—Apparent diffusion constants of 4'-aminopropiophenone through 3 mil Silastic membrane at 24.90° as a function of pH of the drug solutions.

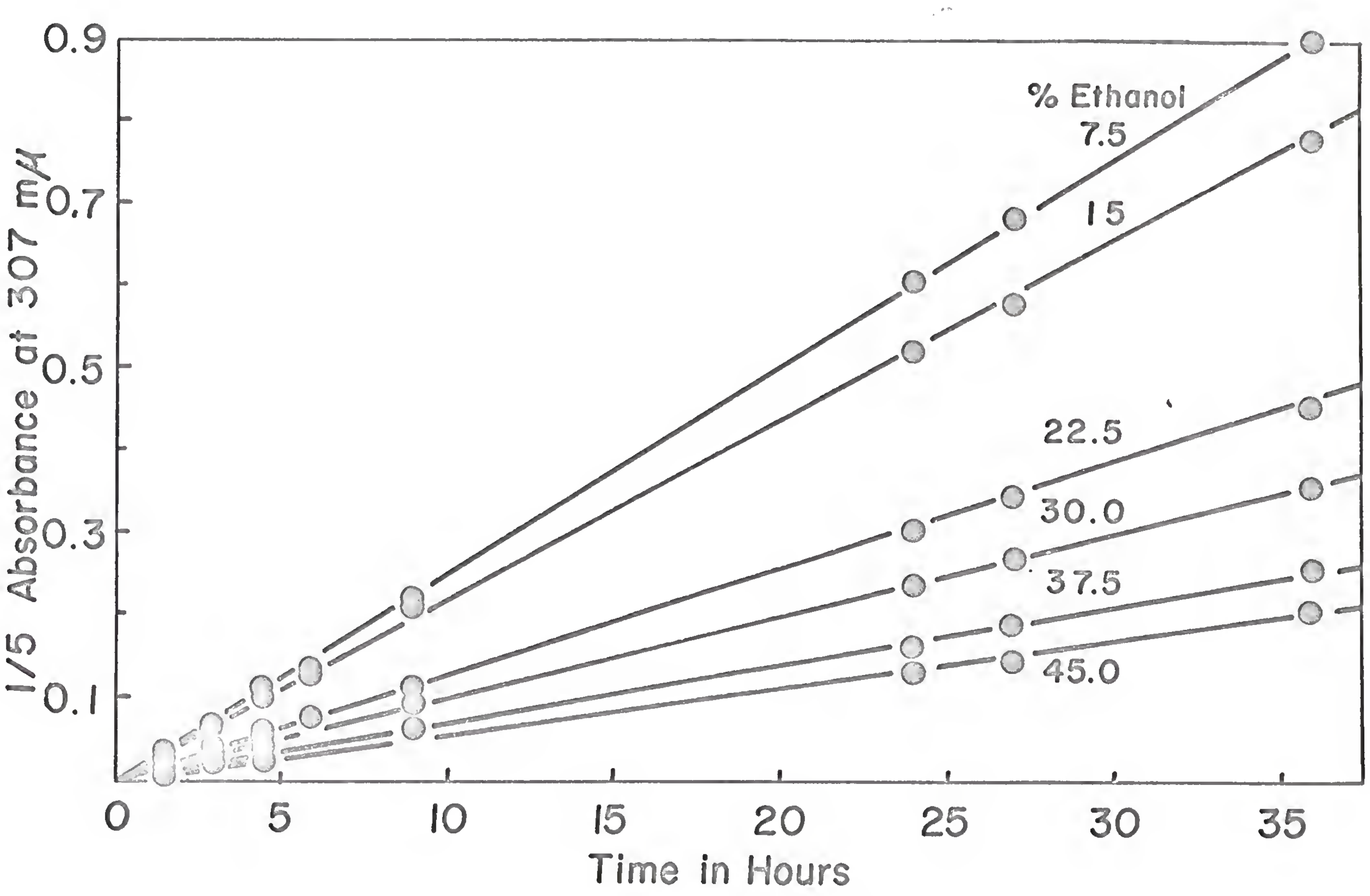


Fig. 13.—Effect of ethanol on the rate of diffusion of 4'-aminopropiophenone through 3 mil Silastic membrane from solutions in phosphate buffer containing varying percentages of ethanol at 25.0°. (The absorbance of the desorbant solution was measured as a function of time.)

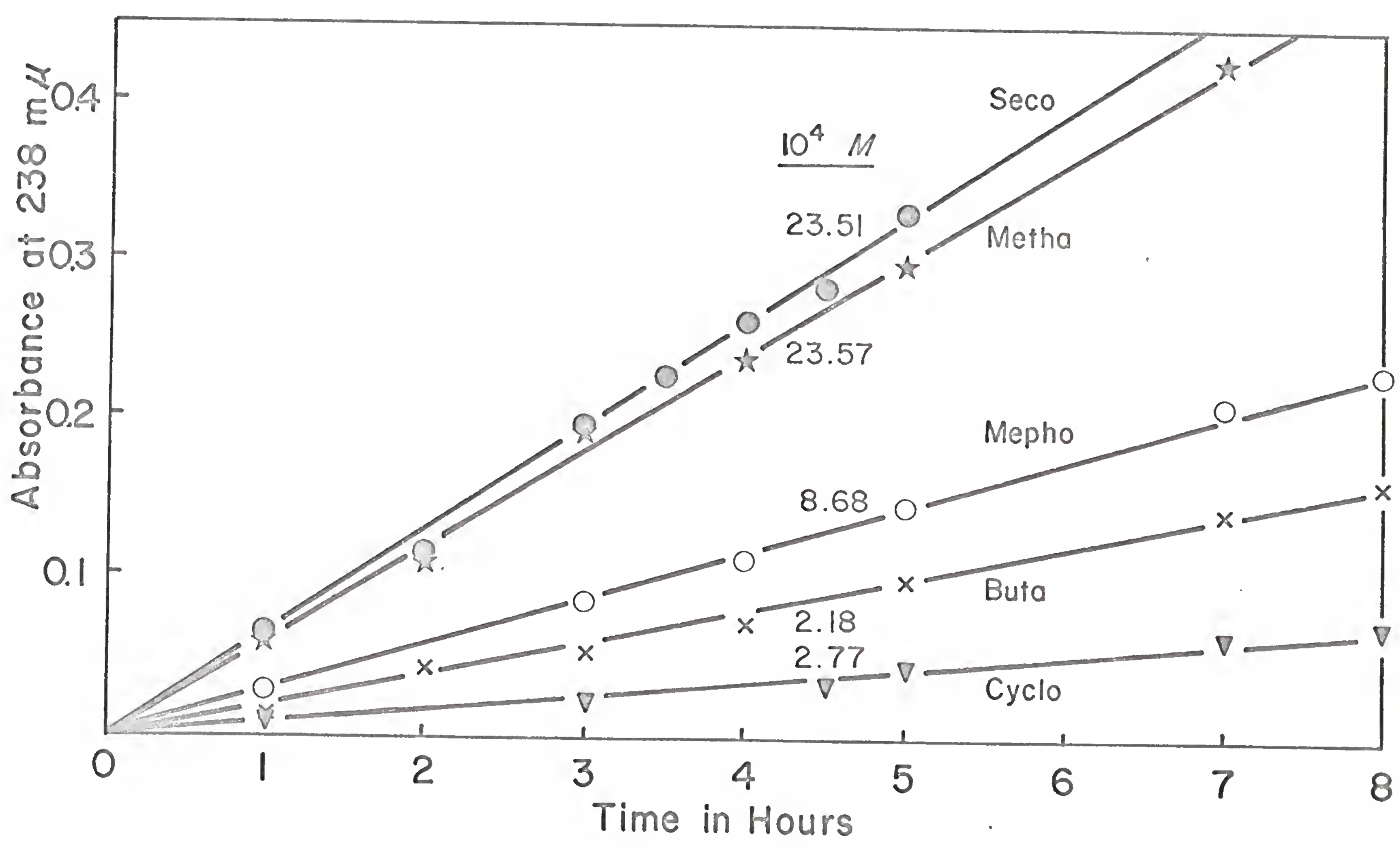


Fig. 14.—Diffusion of barbituric acid derivatives through 3 mil Silastic membrane from solutions in pH 4.7 acetate buffer at 37.3°. (The absorbance of the desorbant solutions was measured as a function of time. (Seco - secobarbital, Metha - metharbital, Mepho - mephobarbital, Buta - Butabarbital, Cyclo - cyclobarbital.)

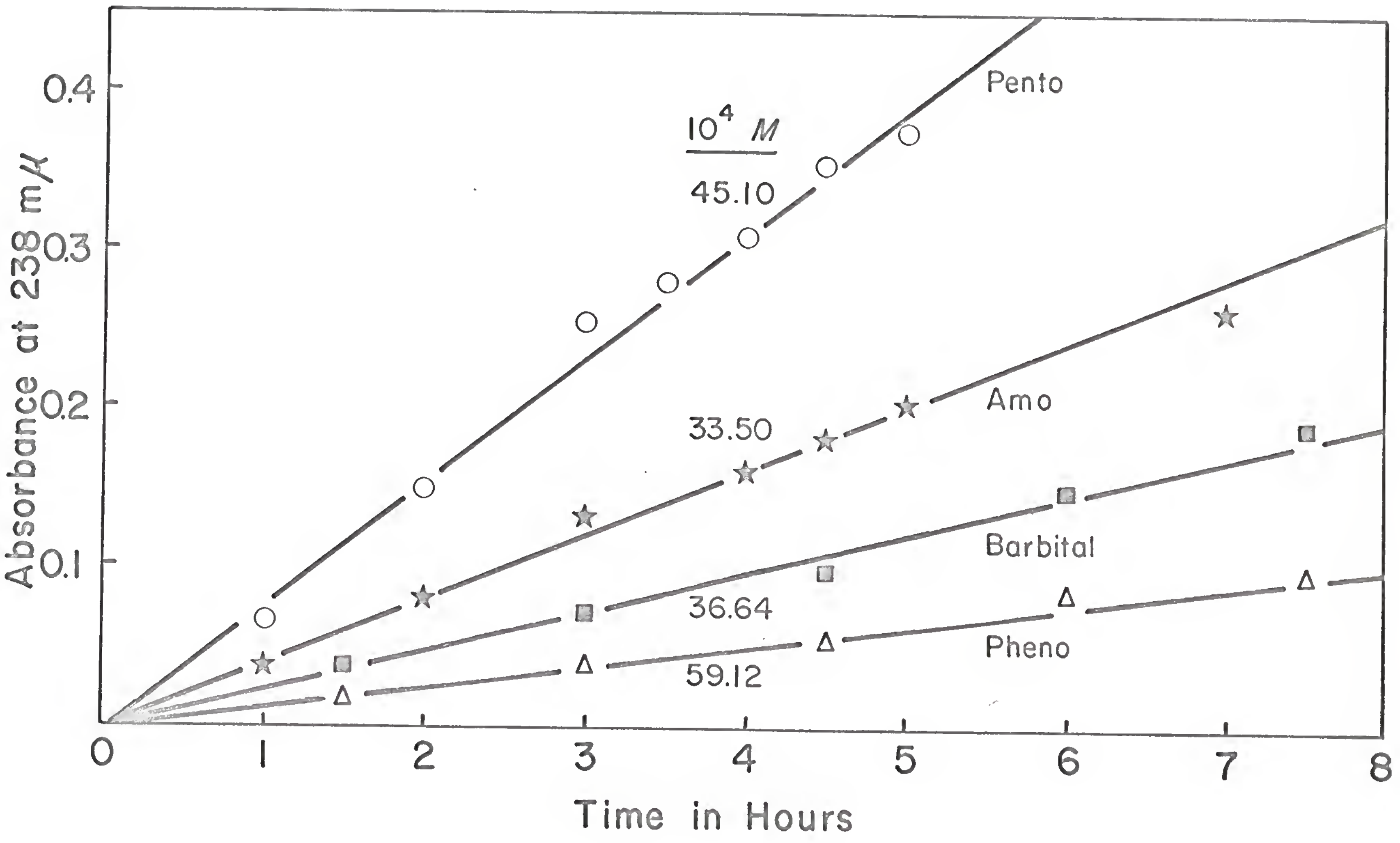


Fig. 15.—Diffusion of barbituric acid derivatives through 3 mil Silastic membrane from solutions in pH 4.7 acetate buffer at 37.3°. (The absorbance of the desorbant solution was measured as a function of time. Pento - pentobarbital, Amo - amobarbital, Pheno - phenobarbital.)

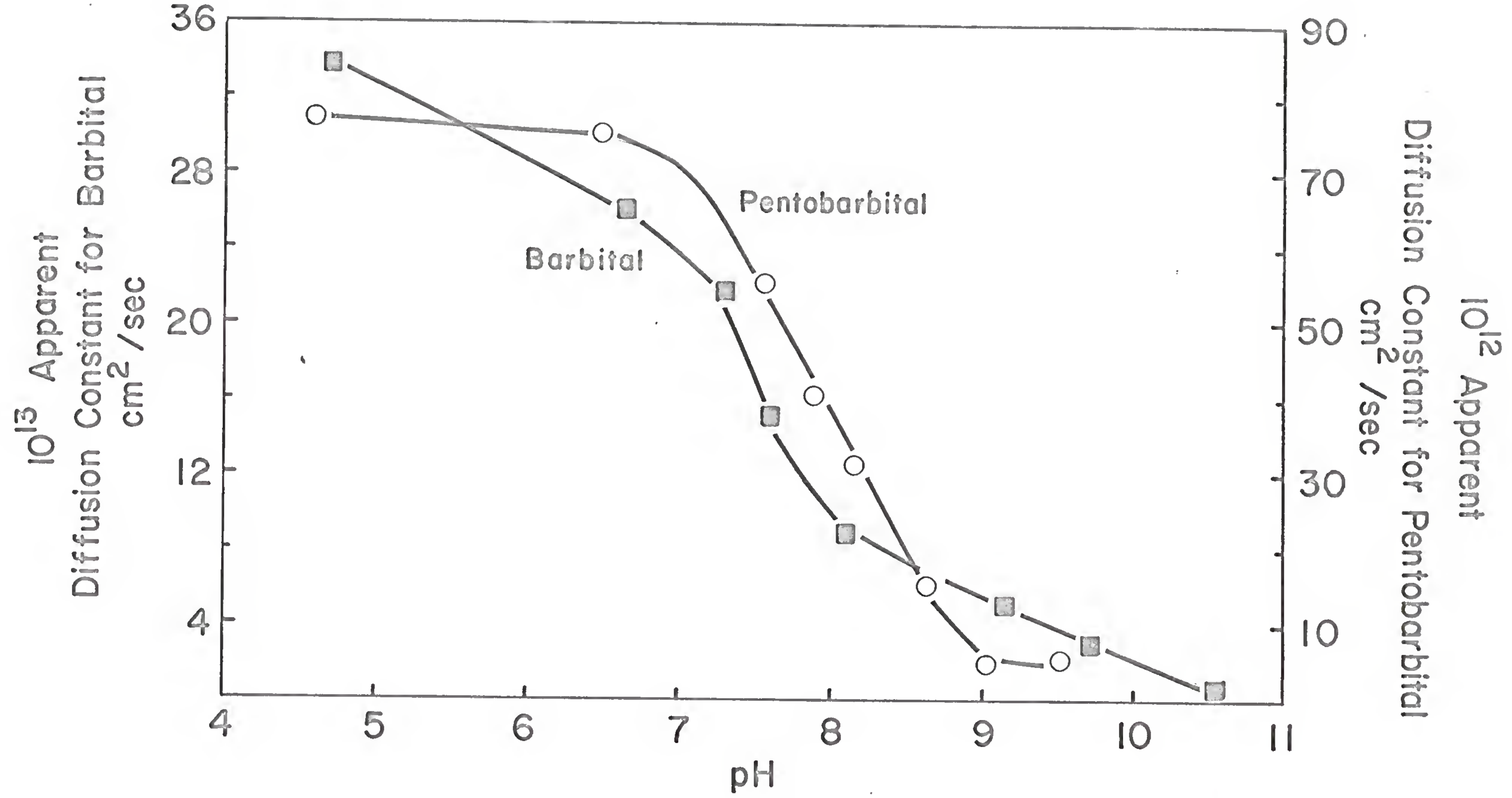


Fig. 16.—Apparent diffusion constants of barbital and pentobarbital through 3 mil Silastic membrane as a function of the pH of the drug solutions.

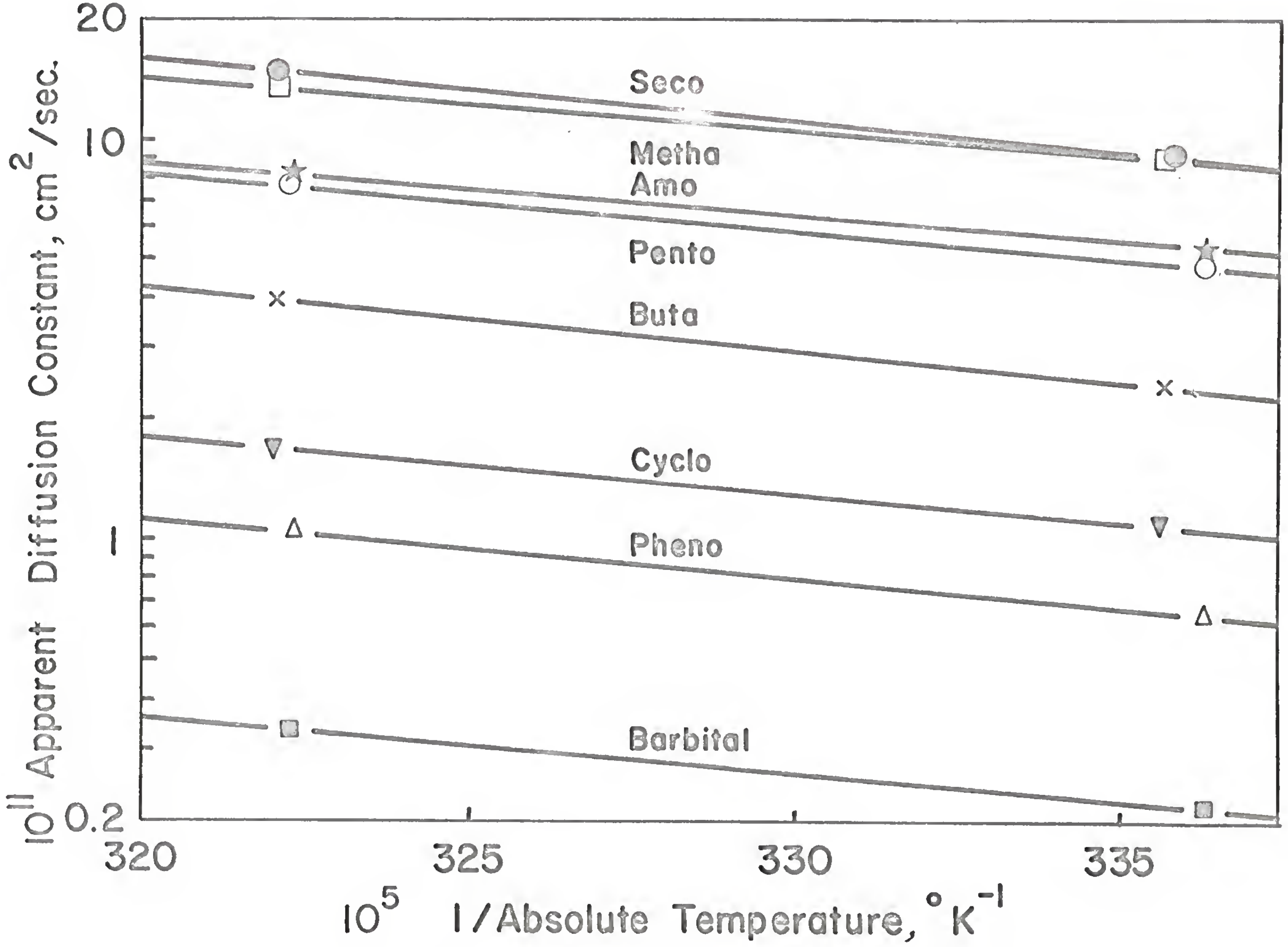


Fig. 17.—Arrhenius plots for the apparent diffusion constants of barbituric acid derivatives from solutions in pH 4.7 acetate buffer through 3 mil Silastic membrane.

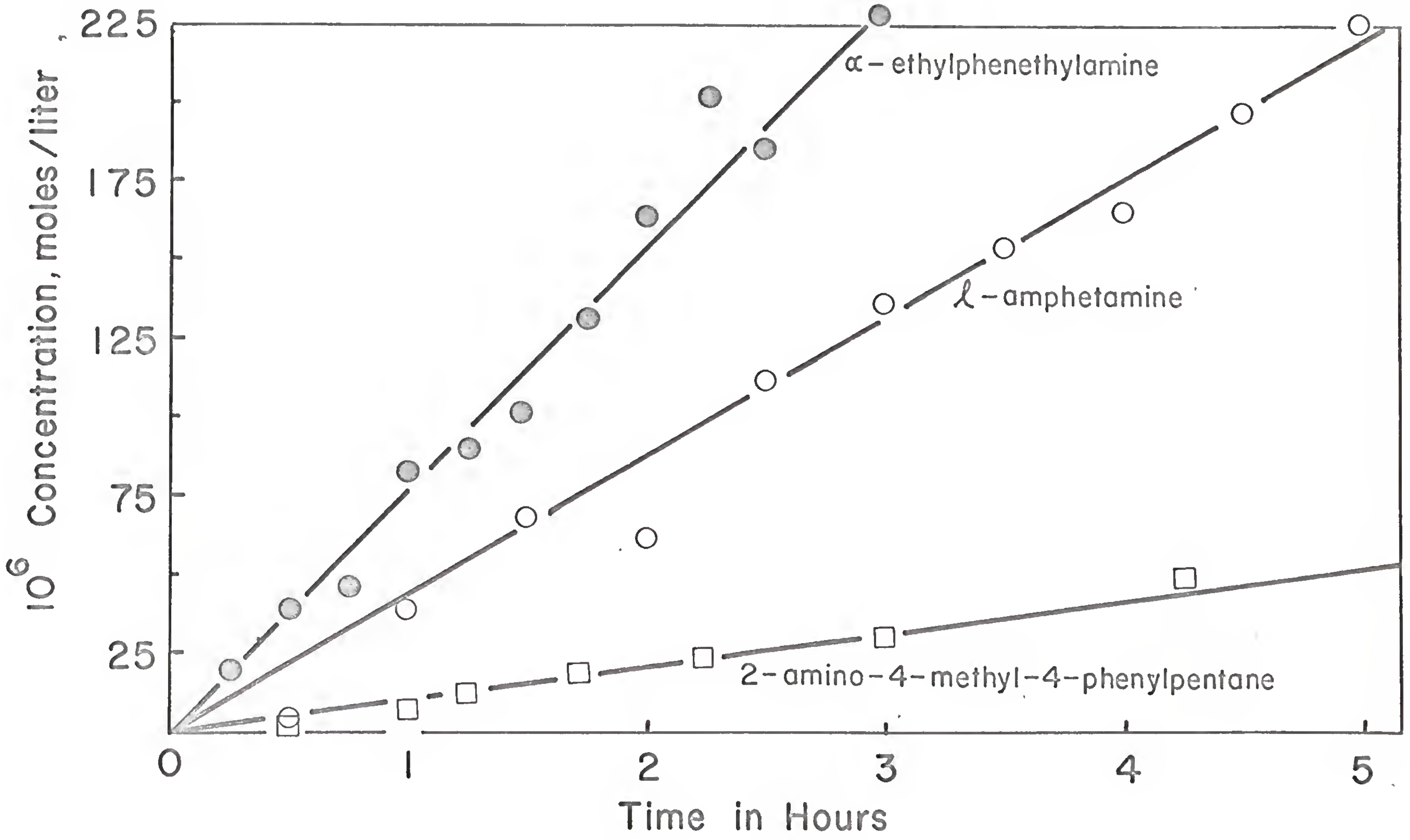


Fig. 18.—Plots for the diffusion of phenylalkylamines from solutions in borate buffer through 3 mil Silastic membrane at 25.0°. (The concentrations were calculated from the absorbances of the desorbant solutions measured as a function of time.)

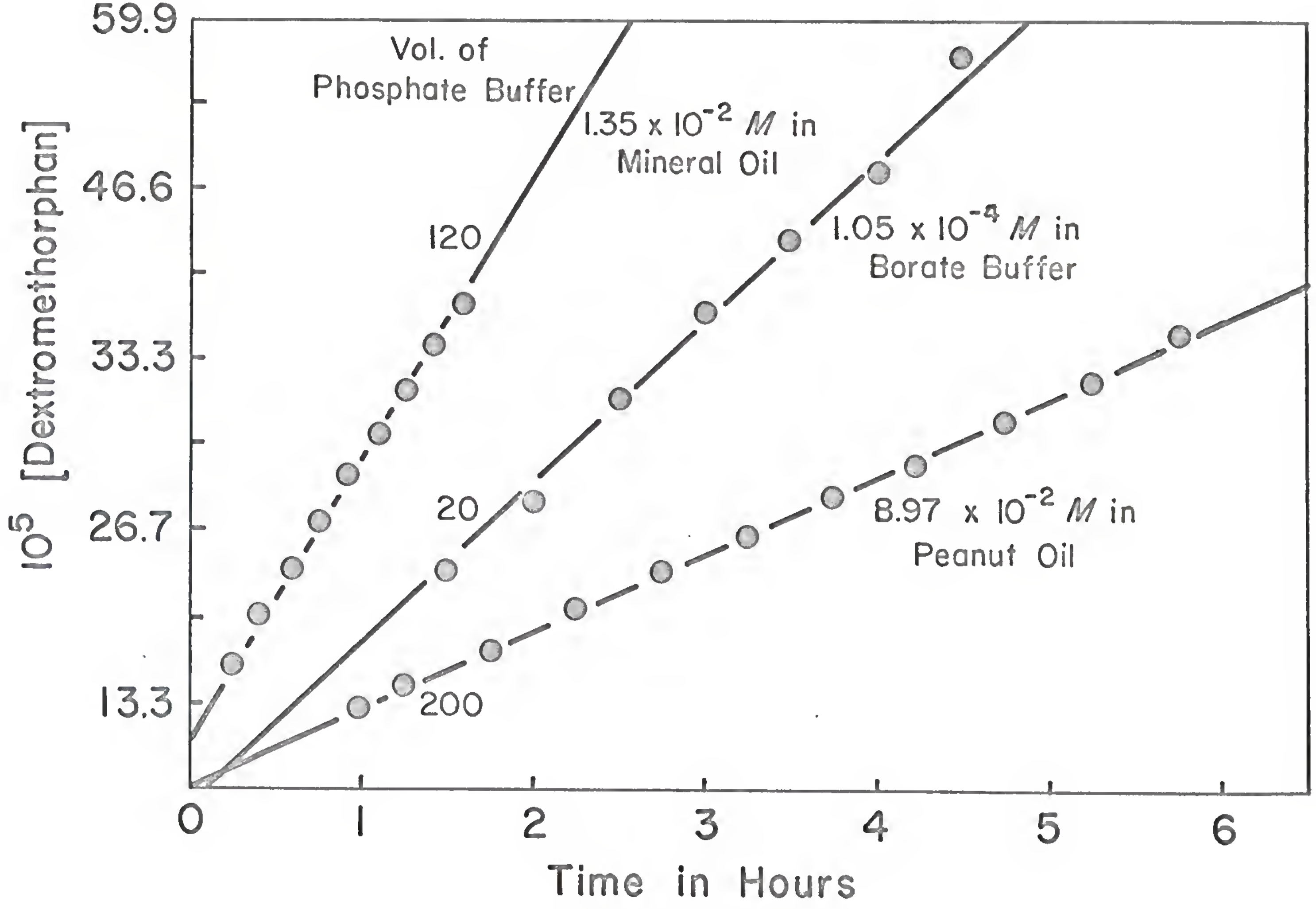


Fig. 19.—Plots for the diffusion of dextromethorphan from solutions in pH 10.1 borate buffer, peanut oil, and mineral oil through 3 mil Silastic membrane at 37.5°. (The concentrations were calculated from the absorbances of the desorbant solutions measured as a function of time.)

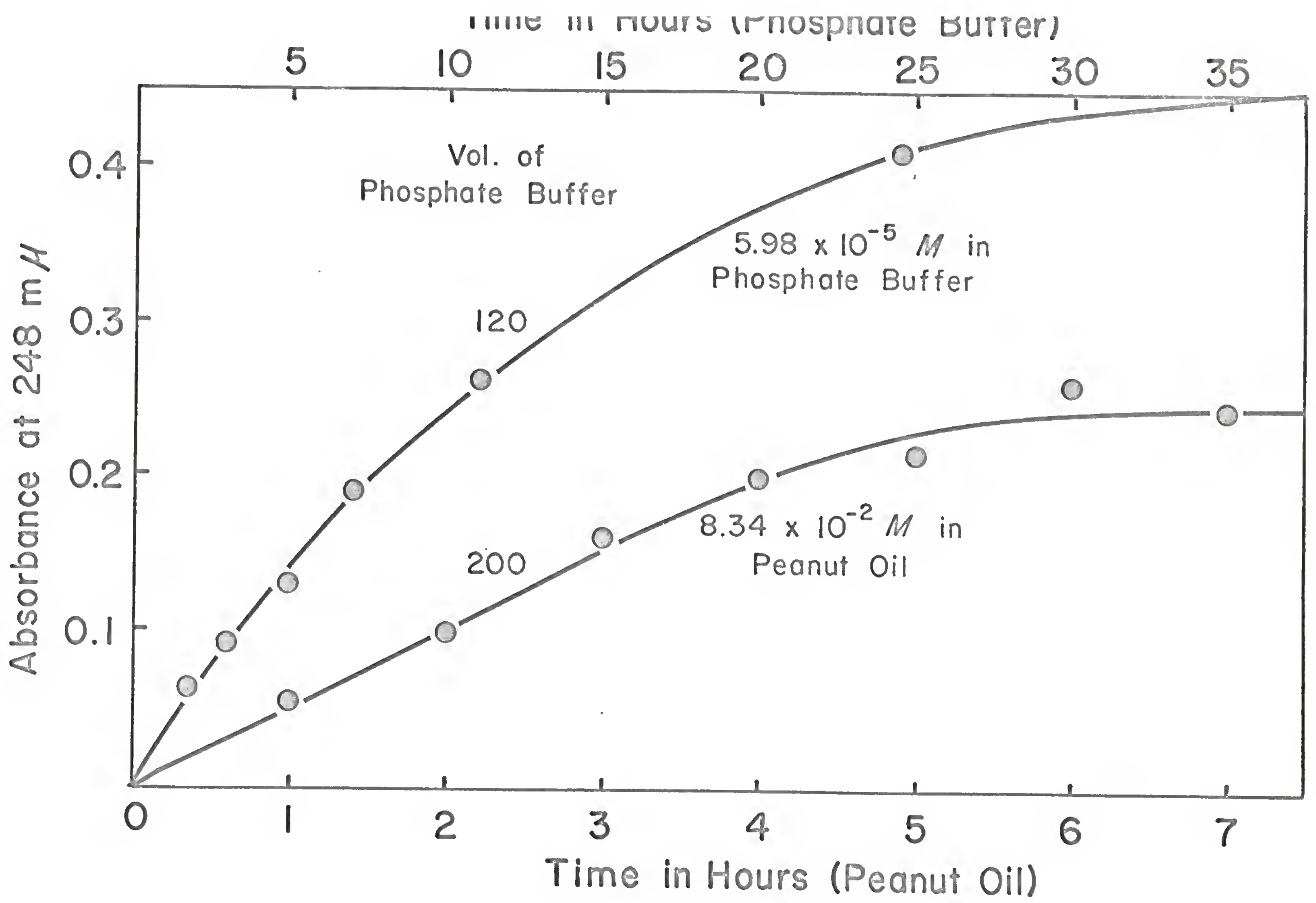


Fig. 20.—Plots for the diffusion of progesterone from solutions in phosphate buffer and peanut oil through 3 mil Silastic membrane at 37.5°. (The absorbance of the desorbant solution was measured as a function of time.)

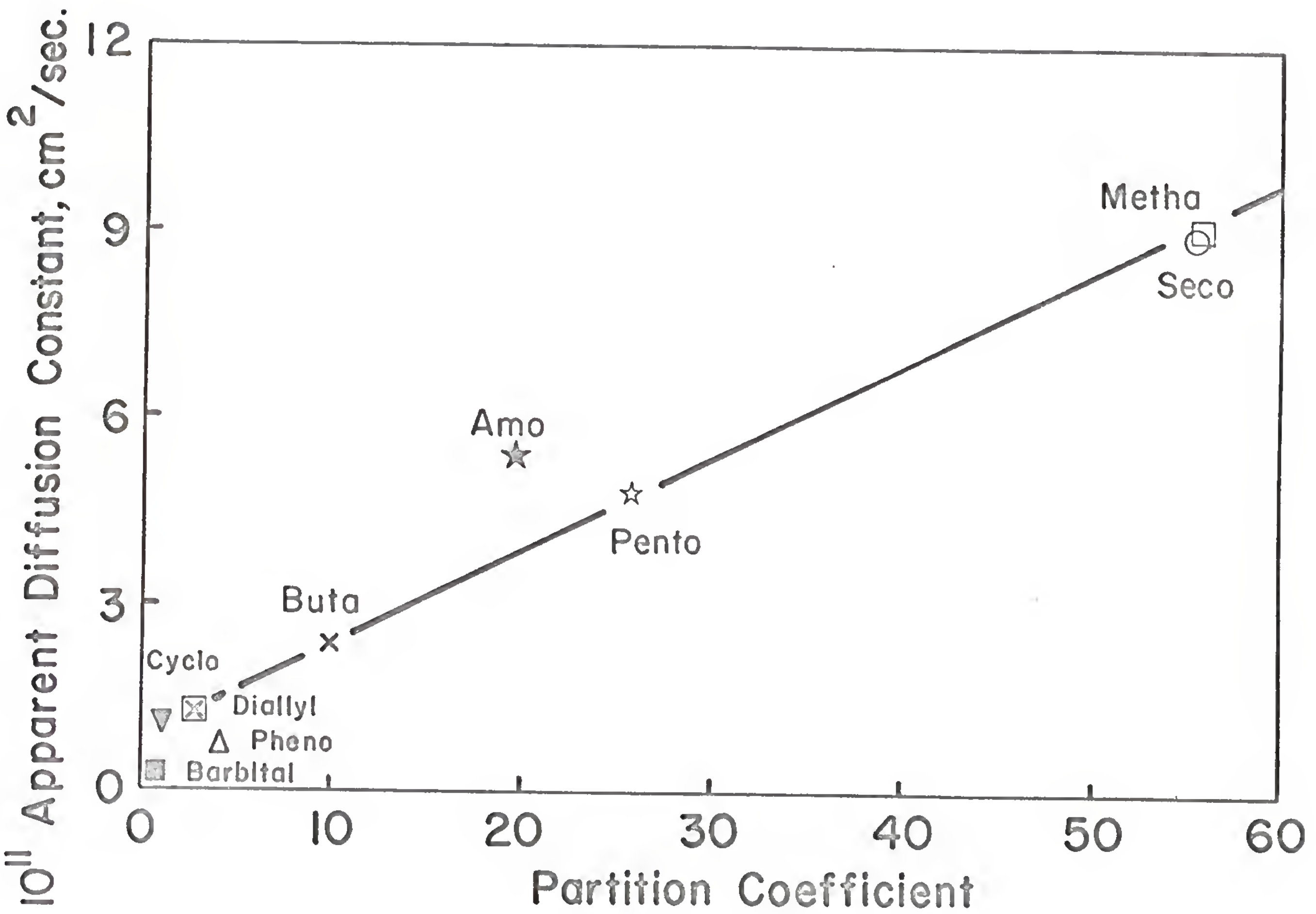


Fig. 21.—Plot of the apparent diffusion constants of barbituric acid derivatives through 3 mil Silastic membrane at 25.0° versus partition coefficients for the compounds between acetate buffer solutions and chloroform. (Seco - secobarbital, Metha - methabarbital, Amo - amobarbital, Pento - pentobarbital, Buta - butabarbital, Cyclo - cyclobarbital, Diallyl - diallylbarbituric acid, Pheno - phenobarbital).

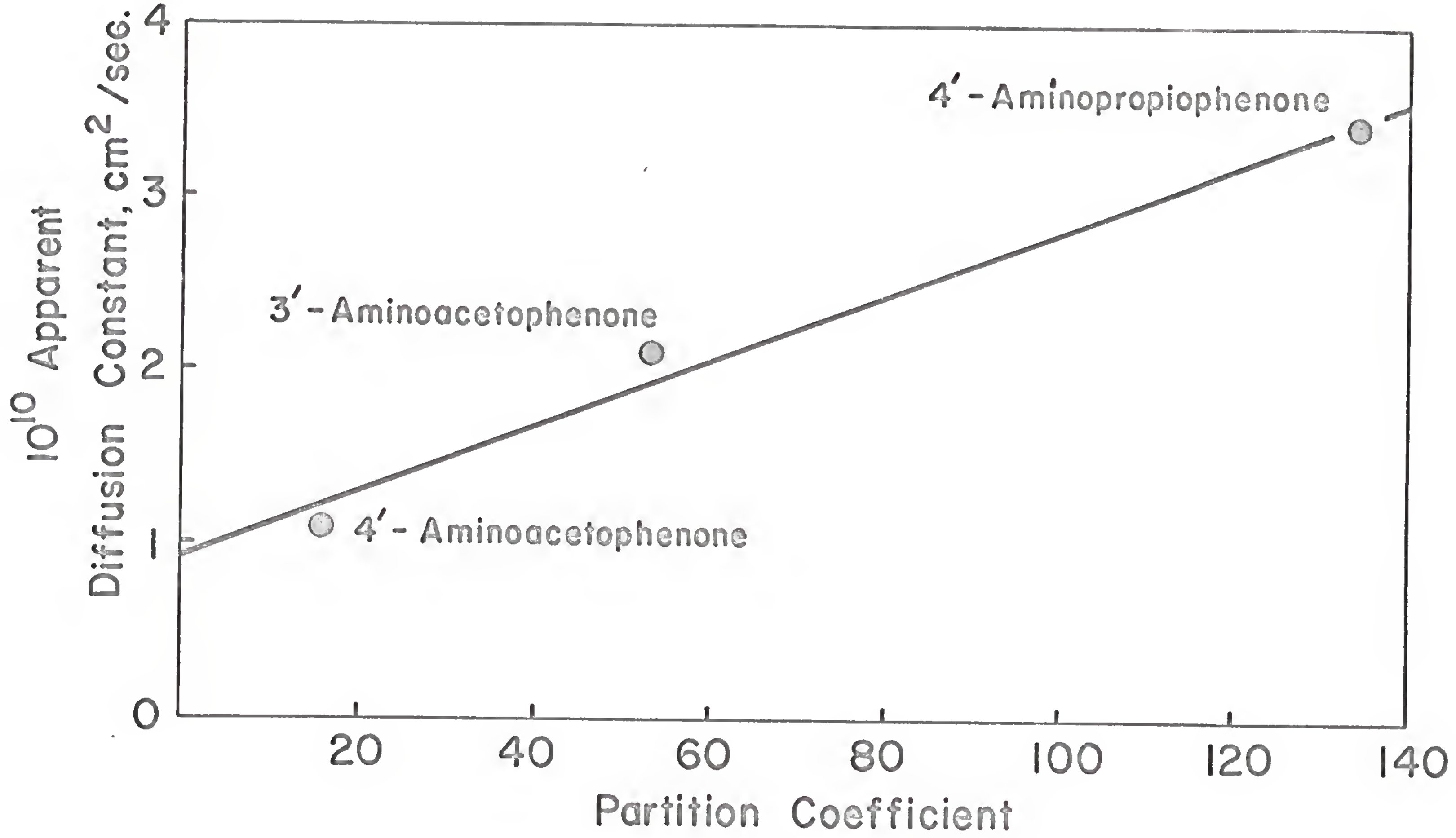


Fig. 22.—Plot of the apparent diffusion constants of aminoalkylphenones through 3 mil Silastic membrane at 25.0° versus the partition coefficients for the compounds between solutions in phosphate buffer and chloroform.

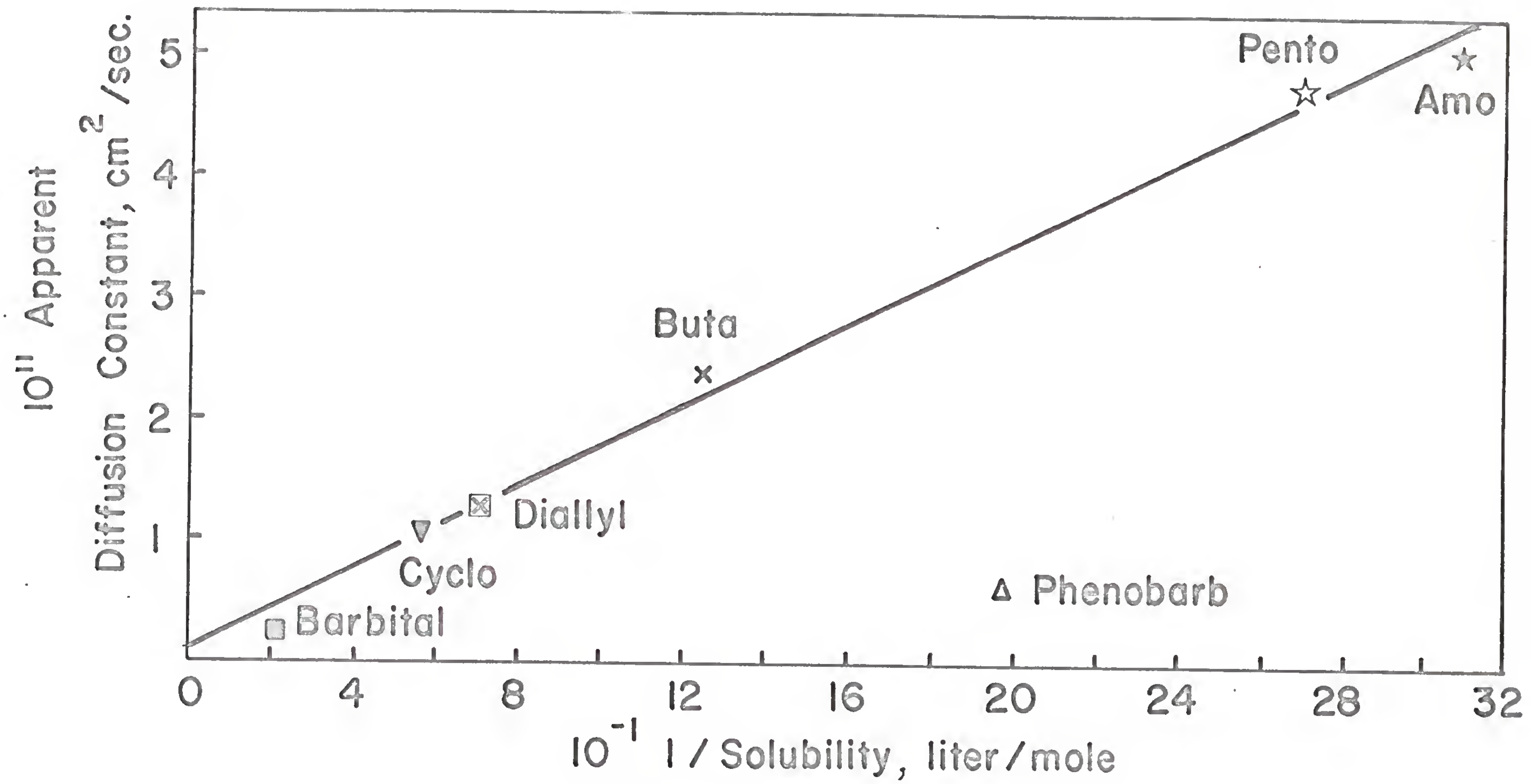


Fig. 23.—Plot of the apparent diffusion constants of barbituric acid derivatives through 3 mil Silastic membrane at 25.0° versus reciprocal of the solubility of the compounds in pH 4.7 acetate buffer solutions at 25.0°.

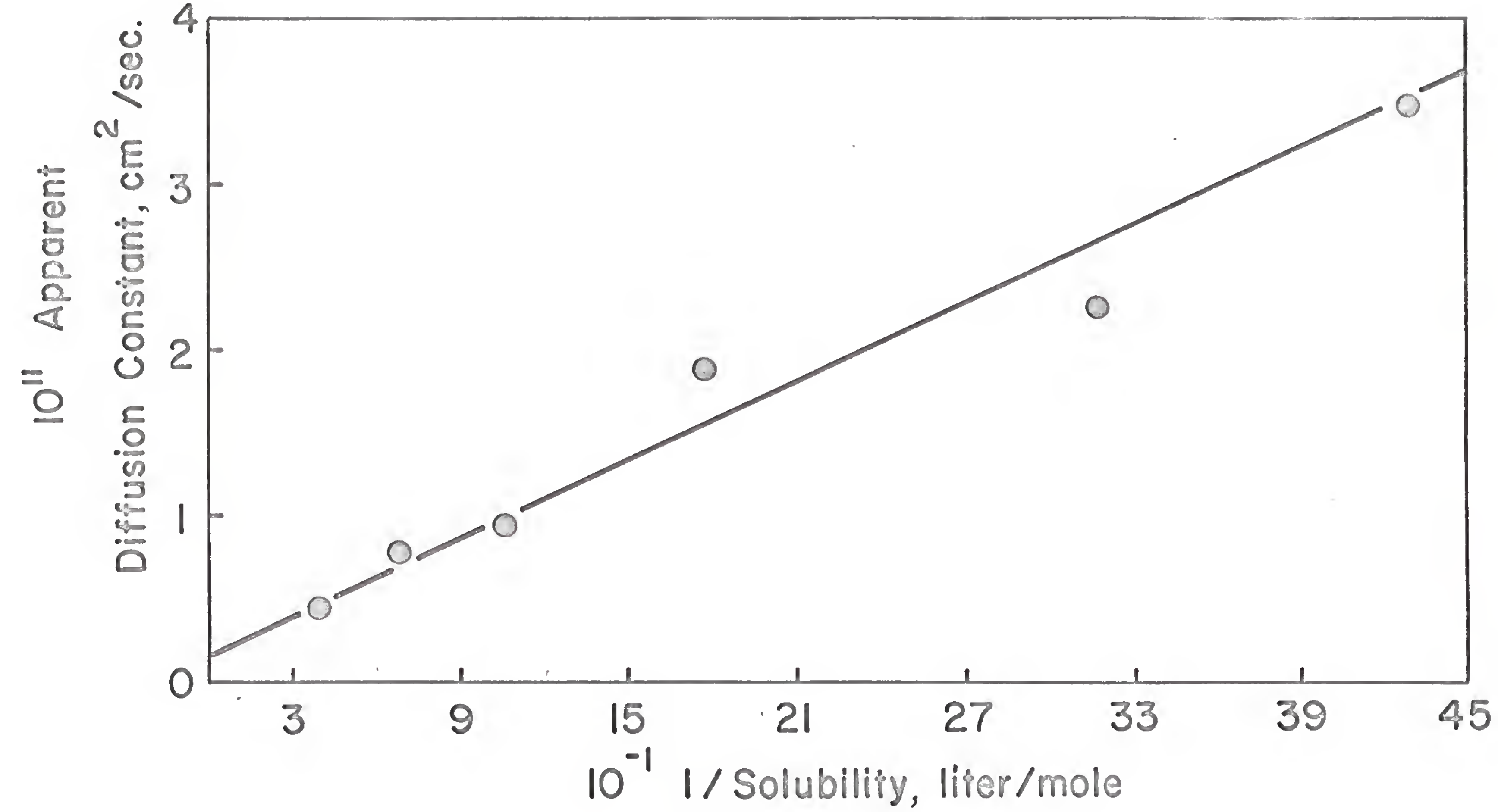


Fig. 24.—Plot of the apparent diffusion constants of 4'-aminopropiophenone from solutions in phosphate buffer containing varying percentages of ethanol versus the reciprocal of solubility in the respective buffer solutions.

C. Derivations and Statistical Analyses

APPENDIX C - I

Derivation of Sutherland and Einstein Equation

If a system is not in equilibrium it will move toward equilibrium and the negative gradient of the chemical potential may be considered the driving force of diffusion.

The force F of diffusion in a rectangular cell in which there is no convection and flow is due to diffusion only in x direction (106)

$$F = -d\mu/dx = -(d\mu/dC)\ (dC/dx) = -(RT/C)\ (dC/dx) \qquad \text{(Eq. 46)}$$

for an ideal solution, since $\mu = \mu_O + RT \ln C$ where μ is the chemical potential, C is the concentration, R is the gas constant and T is the absolute temperature.

According to hydrodynamics the velocity of a particle in a continuous medium is directly proportional to the applied force, and, by definition, the frictional coefficient is the force required to give the particle unit velocity.

$$F/N = fv \qquad \text{(Eq. 47)}$$

where f is the molecular frictional coefficient, v is the velocity, and N is Avogadro's number. Therefore

$$v = F/Nf = -(RT/NfC)\ (dC/dx) \qquad \text{(Eq. 48)}$$

Fick's first law is

$$J = vC = -D\ dC/dx \qquad \text{(Eq. 49)}$$

where J is the amount passing in unit time per unit area and D is the apparent diffusion constant. Therefore

$$-(RT/Nf)\ dC/dx = -D\ dC/dx \qquad \text{(Eq. 50)}$$

hence $$D = RT/Nf \qquad \text{(Eq. 51)}$$

but by Stokes law

$$f = 6\pi\eta r \qquad \text{(Eq. 52)}$$

therefore $$D = RT/6\pi\eta rN \qquad \text{(Eq. 53)}$$

Since the relation between radius r, molecular weight M and partial specific volume $\bar{v}$ is given as

$$M\bar{v}/N = 4/3(\pi r^3) \qquad \text{(Eq. 54)}$$

therefore $$D = RT/6\pi\eta N\ (4\pi N/3M\bar{v})^{1/3} \qquad \text{(Eq. 1)}$$

APPENDIX C - II

Derivation of Fick's Second Law of Diffusion

Fick's first law of diffusion (74)

$$dA/dt = .-D\ dC/dx \qquad \text{(Eq. 4)}$$

states that the increase in the amount of a substance A in time t within a volume element bounded by two parallel planes of area 1 cm.^{2} situated at x and x + dx is given by

$$(dA/dt)_x - (dA/dt)_{x+dx} = D\,[(dC/dx)_{x+dx} - (dC/dx)_x] \qquad \text{(Eq. 55)}$$

where dC/dx is the concentration gradient and D is the apparent diffusion constant. After dividing Eq. 55 by the volume element (dx. 1) in cm.^{3} the increase in concentration with time, in the limit dx$\rightarrow$ 0 is given by

$$dC/dt = D\ d^2C/dx^2 \qquad \text{(Eq. 5)}$$

which is the Fick's second law of diffusion.

APPENDIX C - III

Partial Derivation of Equation For Calculation of Diffusion Constants By Time-lag Method

Fick's second law of diffusion (Appendix C - II) is

$$dC/dt = D' d^2C/dx^2 \qquad \text{(Eq. 5)}$$

where C is the concentration of the diffusing species, D' is the intrinsic diffusion constant, x is the distance into the membrane and t is the time. For particular boundary conditions

$C = C_0$ at $x < 0$ and at all time

$C \sim 0$ at $x > X$ and at all time

$C = 0$ at $X < x < 0$ and at $t = 0$

and assuming equilibrium between membrane and outside phase, the solution obtained for amount A transported through the membrane is

$$A = (D' C_0 t/X) + 2X\pi^2 {}_{n=1}\sum (C_0 \cos n\pi/n^2)(1 - e^{-D^2\pi^2 t/X^2}) \qquad \text{(Eq. 56)}$$

At $t = \infty$ this equation reduces to

$$A = D'C_0 t/X - C_0 X/6 \qquad \text{(Eq. 57)}$$

$$A = (D'C_0/X)\ (t - X^2/6D') \qquad \text{(Eq. 58)}$$

However if C_0 is the concentration in the membrane related to the concentration C'_0 in the aqueous solution by partition coefficient K_p as

$$K_p = C_0/C'_0 \qquad \text{(Eq. 59)}$$

The C_0 term in Eq. 55 may be substituted by C'_0K_p to obtain

$$A = D'C'_0K_pt/X - C'_0K_pX/6 \qquad \text{(Eq. 60)}$$

$$A = (D'C'_0K_p/X)\ (t - X^2/6D') \qquad \text{(Eq. 61)}$$

$$A = (DC'_0/X)\ (t - X^2/6D') \qquad \text{(Eq. 62)}$$

where D is the apparent diffusion constant given by

$$D = D'K_p \qquad \text{(Eq. 37)}$$

APPENDIX C - IV

Derivation of Equations For Quasi-steady State Diffusion

A) Let C_1 and C_2 be the concentrations of a diffusing species in V_1 and V_2 liters of two solutions separated by a membrane with a surface area of S $cm.^2$ and thickness of X cm. Let the concentrations of the diffusing species in the monolayers of the membrane be C_1' and C_2' related to the concentrations in the aqueous solutions in contact with the monolayers by partition coefficients K_{p1} and K_{p2} as

$$C_1' = C_1K_{p1} \quad \text{and} \quad C_2' = C_2K_{p2} \qquad \text{(Eq. 63)}$$

The following equations hold

$$dC_1/dt = (D'S/XV_1)\,(C_2' - C_1') \qquad \text{(Eq. 64)}$$

$$dC_2/dt = -(D'S/XV_2)\,(C_2' - C_1') \qquad \text{(Eq. 65)}$$

where D' is the intrinsic diffusion constant. When the relations in Eq. 63 are substituted in Eqs.64 and 65

$$dC_1/dt = (D'S/XV_1)\,(C_2K_{p2} - C_1K_{p1}) \qquad \text{(Eq. 66)}$$

$$dC_2/dt = -(D'S/XV_2)\,(C_2K_{p2} - C_1K_{p1}) \qquad \text{(Eq. 67)}$$

When Eq. 66 is subtracted from Eq. 67 the result is

$$d(C_2 - C_1)dt = -(D'S/X)\,(1/V_1 + 1/V_2)\,(C_2K_{p2} - C_1K_{p1}) \qquad \text{(Eq. 68)}$$

If the solutions on the two sides of the membrane are the same then

$$K_{p1} = K_{p2} = K_p \qquad \text{(Eq. 69)}$$

and Eq. 68 reduces to

$$d(C_2 - C_1)/dt = -(D'SK_p/X)\ (1/V_1 + 1/V_2)\ (C_2 - C_1) \qquad \text{(Eq. 70)}$$

This equation on integration yields

$$(C_2 - C_1) = C_0 e^{-(D'SK_p/X)(1/V_1 + 1/V_2)t} \qquad \text{(Eq. 71)}$$

when $C_2 = C_0, C_1 = 0$ at $t = 0$.

If $V_1 = V_2 = V$ Eq. 71 reduces to

$$(C_2 - C_1) = C_0\, e^{-(2D'SK_p/VX)t} \qquad \text{(Eq. 72)}$$

The logarithmic form of Eq. 72 is

$$\log\ (C_2 - C_1/C_0) = -(0.869\ D'SK_p/VX)t \qquad \text{(Eq. 73)}$$

B) For the initial conditions of $C_1 = 0, C_2 = C_0$ at $t = 0$

$$V_1C_1 + V_2C_2 = V_2C_0 \qquad \text{(Eq. 74)}$$

therefore $C_2 = (V_2C_0 - V_1C_1)/V_2$ (Eq. 75)

when Eq. 75 is substituted in Eq. 66 the result is

$$dC_1/dt = (D'S/XV_1)[(K_{p2}(V_2C_0 - V_1C_1)/V_2) - C_1K_{p1}] \qquad \text{(Eq. 76)}$$

$$dC_1/dt = (D'S/XV_1)[K_{p2}C_0 - (K_{p2}V_i + K_{p1}V_2)C_1/V_2)] \qquad \text{(Eq. 77)}$$

Equation 77 when integrated between the limits of C_1 and 0, and t and 0, yields

$$(V_2/(K_{p2}V_1 + K_{p1}V_2)\ln[K_{p2}C_0/K_{p2}C_0 - ((K_{p2}V_1 + K_{p1}V_2)C_1/V_2)] = (D'S/XV_1)t \qquad \text{(Eq. 78)}$$

If $V_1 = V_2 = V$ and $K_{p1} = K_{p2} = K_p$, Eq. 78 reduces to

$$1/2K_p[\ln(C_0/(C_0 + 2C_1))] = (D'S/XV)t \qquad \text{(Eq. 79)}$$

Therefore $$\log (C_0/(C_0 + 2C_1)) = (0.896\ D'K_pS/XV)t \qquad \text{(Eq. 80)}$$

C) If Ceq. is the equilibrium concentration of the solutions in the two compartments then

$$(V_1 + V_2)\ \text{Ceq.} = V_1C_1 + V_2C_2 \qquad \text{(Eq. 81)}$$

or $$C_2 = ((V_1 + V_2)\ \text{Ceq.}/V_2) - V_1C_1/V_2 \qquad \text{(Eq. 82)}$$

When Eq. 82 is substituted in Eq. 71 the result is

$$[(V_1 + V_2/V_2)\ \text{Ceq.} - (V_1C_1/V_2) - C_1] = C_0e^{-(D'SK_p/X)(1/V_1 + 1/V_2)t} \qquad \text{(Eq. 83)}$$

Equation 83 on rearrangement of terms becomes

$$((\text{Ceq.} - C_1/C_0) = (V_2/(V_1 + V_2))\ e^{-(D'SK_p/X)\ (V_1 + V_2/V_1V_2)t} \qquad \text{(Eq. 84)}$$

The logarithmic form of Eq. 84 is

$$\log (\text{Ceq.} - C_1/C_0) = \log[(V_2/(V_1 + V_2))] - (D'SK_p/2.303X)((V_1 + V_2)/V_1V_2)t \qquad \text{(Eq. 85)}$$

APPENDIX C - V

Berthier Method for Calculation of Diffusion Constants

The method is based on the solution of the equation (71)

$$dC/dt = D\ d^2C/dx^2 \qquad \text{(Eq. 5)}$$

when $C = 0$ for $X > x > -X$ at $t = 0$ and a boundary condition that the rate at which the solute leaves the solution is equal to that at which it enters the sheet over the surfaces $x = \pm X$

$$M_t/M \quad = 1 - \sum (2\alpha(1 - \alpha)/1 + \alpha + \alpha^2\ q^2)\ \exp. - Dq_n^2\ t\ /\ X^2$$

(Eq. 86)

where M_t is the total amount of solute in the sheet at time t and M_∞ is the corresponding quantity after infinite time. Also q_n's are the non-zero positive roots of $\tan q_n = -\alpha q_n$ (Eq. 87)
and α is the ratio of the volumes of the solution and sheet.

The procedure used is to plot M_t/M_∞ as obtained experimentally against the square root of time t. The final percent uptake of the solute by the polymer membrane from the solution at equilibrium is noted. Berthier (79) has plotted the Eq. 86 as M_t/M_∞ for several percent uptake values against Dt/X^2. These theroretical curves are used for calculation of D as follows

$$M_t/M_\infty = S_e t^{\frac{1}{2}} \qquad \text{and} \qquad M_t/M_\infty = S_t(Dt/X^2)^{\frac{1}{2}} \qquad \text{(Eq. 88)}$$

where S_e and S_t are the slopes of the experimental and theoretical plots.

When M_t/M_∞ (theoretical) = M_t/M_∞ (experimental) (Eq. 89)

$$D = S_e^2 X^2 / S_t^2 \qquad \text{(Eq. 90)}$$

All the terms in the Eq. 90 except D are known and hence D can be calculated.

APPENDIX C - VI

Statistical Analysis of Thickness Measurements Obtained on 3 mil Silastic Membranes

# of reading	Measured Thickness Obtained by Difference (X)						
1	3.0	3.0	3.0	2.9	3.0	2.5	3.0
2	2.9	3.3	3.0	3.0	3.1	2.9	2.8
3	3.2	2.9	3.2	3.1	3.2	2.8	2.9
4	3.0	3.1	3.0	2.9	3.0	2.7	3.2
5	3.1	2.9	3.0	3.0	3.0	2.4	2.6
6	3.0	2.9	3.3	2.8	3.0	2.8	3.3
7	3.1	2.9	3.0	3.0	2.9	2.4	3.2
8	3.1	3.0	2.9	2.9	3.1	2.7	2.9
9	3.1	3.0	3.1	2.9	2.9	2.7	2.8

$\sum X = 186.30$ $\bar{X} = 2.96$

$\sum X^2 = 553.08$ $(\sum X)^2/n = 550.9157$

Standard deviation = $S = \sqrt{1/(n-1)[\sum X^2 - (\sum X)^2/n]} = 0.1868$

Estimated Standard Deviation = $S_{\bar{X}} = S/(n)^{\frac{1}{2}} = 0.0235$

From Tables $t_{(0.05)(60)} = 2.00$

Hence at 95% confidence level the mean thickness varies between

$$2.96 \pm 2.00 \times 0.0235 = 2.96 \pm 0.0470$$

Coefficient of Variation = $100\ S/\bar{X} = 6.42\%$

APPENDIX C - VII

Regression Analysis of Raw Data for
Diffusion of 4'-Aminopropiophenone

Hrs. (X)	Absorbance (Y)					
2	1.170	1.120	1.160	1.035	1.045	$\sum X = 20$
3	1.785	1.595	1.700	1.435	1.595	
4	2.390	2.310	2.300	1.975	2.165	$\sum X^2 = 90$
5	2.800	2.575	2.660	2.350	2.525	
6	3.315	3.010	3.265	2.795	3.060	$(\sum X)^2/n = 80$
$\sum Y$	11.460	10.610	11.085	9.590	10.390	$x^2 = \sum X^2 - (\sum X)^2/n = 10$
$\overline{Y}$	2.292	2.122	2.217	1.918	2.078	$\overline{X} = 4$
$\sum XY$	51.145	47.200	49.510	42.795	46.520	
$\frac{\sum X . \sum Y}{n}$	45.840	42.440	44.340	38.360	41.560	
xy	5.305	4.760	5.170	4.435	4.960	$= \sum XY - \sum X \sum Y/n$
$m = xy/x^2$	0.5305	0.4760	0.5170	0.4435	0.4960	
Intercept b	0.170	0.218	0.149	0.144	0.094	$= \overline{Y} - m\overline{X}$
Y_i^2	29.0964	24.8252	27.2614	20.3656	24.0625	
$(Y_i)^2/n$	26.2663	22.5144	24.5754	18.3936	21.5904	
y^2	2.8301	2.3108	2.6860	1.972	2.4721	$= \sum Y^2 - (\sum Y)^2/n$
S.S. = mxy	2.8143	2.2658	2.6729	1.9669	2.4602	S.S. due to regression
	0.0158	0.0450	0.0131	0.0051	0.0119	S.S. Deviation from Regression = $y^2 - mxy$
$S^2_{Y.X}$	0.0053	0.0150	0.0044	0.0017	0.0039	$y^2 - mxy/n-2$
S_b^2	0.00954	0.0270	0.00812	0.00306	0.00702	$= S^2_{YX}(1/n + \overline{X}^2/x^2)$
S_b	0.097	0.164	0.091	0.055	0.0838	
b/S_b	1.753	1.329	1.637	2.618	1.122	$= t$

From the Tables $t_{(0.025)(3)} = 3.182$

Hence at 5% level of significance the hypothesis that the intercepts go through the origin cannot be rejected.

APPENDIX C - VIII

Analysis of Variance of Data[a] Collected to Show the Reproducibility of Rates of Diffusion of 4'-Aminopropiophenone through 3 mil Silastic Membrane.

Days	Runs	Slopes of Concentration versus Time Moles/liter. Hr.						
		1	2	3	4	5	X	$\bar{X}$
1		0.491	0.482	0.467	0.404	0.425	2.269	0.4538
2		0.531	0.476	0.517	0.444	0.496	2.464	0.4928
3		0.695	0.452	0.501	0.518	0.506	2.672	0.5344
4		0.537	0.483	0.434	0.471	0.509	2.434	0.4868
5		0.509	0.493	0.550	0.592	0.422	2.566	0.5132
Sum		2.763	2.386	2.469	2.429	2.358	12.405	

Correction = C = $(12.405)^2/25 = 6.155361$

S.S. Days = $(2.269)^2 + \ldots\ldots + (2.566)^2/5 - C = 0.018229$

S.S. Replicates = $(2.763)^2 + \ldots\ldots + (2.358)^2/5 - C = 0.021305$

Total S.S. = $(0.491)^2 + \ldots\ldots + (0.422)^2 - C = 0.085756$

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[a] Diffusion of 4'-aminopropiophenone from saturated solution in phosphate buffer through 3 mil Silastic membrane into 200 ml. of 0.12 N. HCl.

Analysis of Variance Table

Source of Variation	D.F.	S.S.	Mean Square	F ratio
Replicates	4	0.021305	0.005326	1.84 N.S.[b]
Days	4	0.018229	0.004557	1.58 N.S.[b]
Error	16	0.046222	0.0028888	
Total	24	0.085756		

F ratio for replicates = 0.005326/0.002889 = 1.84

F ratio for days = 0.004557/0.002889 = 1.58

From tables $F_{4,16(0.05)} = 3.01$

Therefore differences between the values of replicates on one day and on different days are not significant.

Component Analysis

Source of Variation	D.F.	Mean Square	Parameters estimated
Replicates	4	0.005326	$\sigma^2_E + 4\sigma^2_R$
Days	4	0.004557	$\sigma^2_E + 4\sigma^2_D$
Error	16	0.002889	σ^2_E

σ^2_E = Estimated random variance associated with diffusion experiment and does not include the variance associated with replicates and days.

σ^2_R = Estimated variance for variation among replicates = (0.005326 - 0.002889)/4 = 0.000609

σ^2_D = Estimated variance for variation among days = (0.004557 - 0.002889)/4 = 0.00417

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[b] N.S. = Not Significant

σ^2_{Av} = Estimate of variance for average of 5 x 5 slope values

$= \sigma^2_E/25 + \sigma^2_D/5 = 0.000108$

Means

$\sum X = 2.481 \qquad \bar{X} = 0.4962$

$\sum X^2 = 1.2347181$

$(\sum X)^2/n = 1.2310722$

$S^2 = 0.0036459/(5 - 1) = 0.0009115$

Standard deviation = 0.0302

Coefficient of variation = 0.0302 × 100/0.4962

= 6.09%

Estimated standard deviation of $\bar{X} = S_{\bar{X}} = S/5^{\frac{1}{2}} = 0.0135$

From Tables $t_{(0.05)(4)} = 2.776$

$\bar{X} = 0.4962 \pm 2.776 \times 0.0135$

$= 0.4962 \pm 0.0375$

APPENDIX C - IX

Effect of Ionic Strength on Diffusion of 4'-Aminopropiophenone through 3 mil Thick Silastic Membrane into 200 ml. of 0.12 N HCl at 23.0° as a Function of Ionic Strength of Drug Solution in Phosphate Buffer

Ionic Strength (μ)	0.102	0.198	0.300	0.402
Slopes of Plots of Concentration vs. Time 10^5 moles/liter - Hr.	1.245	1.239	1.303	1.312
Concentration of Solution 10^3 moles/liter	1.804	1.780	1.780	1.773
Specific Rates of Diffusion[a] 10^2 Hr.$^{-1}$	6.90	6.96	7.32	7.34

[a] Slopes of Concentration versus time normalized with respect to the concentration of the drug solution.

X = Specific rate of diffusion × 10^2

$n = 4 \quad \sum X = 28.52 \quad \overline{X} = 7.13$

$\sum X^2 = 203.5096 \quad (\sum X)^2/n = 213.3476$

$$\text{Variance} = S^2 = 1/(n - 1)[\sum X^2 - (\sum X)^2/n]$$

$$= 0.0540$$

Standard deviation = 0.2324

Coefficient of variation = $100 \times S/\overline{X} = 3.24\%$

Mean = 7.13×10^{-2} Standard deviation = $\pm 0.2324 \times 10^{-2}$

Coefficient of variation = 3.24%

APPENDIX C - X

Specific Rates of Diffusion of 4'-Aminopropiophenone Obtained as a Function of Hydrostatic Pressure Exerted On Silastic Membrane at 25.0°

Levels of Suction Tube With Respect to Level of Solution in Beaker	0"	½"	1"	3"
Slopes of Plots of Concentration vs. Time 10^5 moles/liter - Hr.	1.423	1.463	1.394	1.450
Concentration of Solutions 10^3 moles/liter	1.698	1.698	1.661	1.720
Specific Rates of Diffusion[a] 10^3 Hr.$^{-1}$	8.43	8.66	8.39	8.43

[a] Slopes of concentration versus time/concentration of diffusing solution.

X = Specific rate of diffusion × 10^3 = Slopes of plots of conc. vs. time/concentration.

$n = 4$ $\quad \sum X = 33.910$ $\quad \overline{X} = 8.4775$

$\sum X^2 = 287.5175$

$(\sum X)^2/n = 287.4720$

$$\text{Variance} = S^2 = 1/(n - 1)[\sum X^2 - (\sum X)^2/n]$$

$$= 0.01517$$

Standard deviation = $S = 0.1232$

Coefficient of variation = $S/\overline{X} \times 100 = 1.45$

Mean = 8.4775×10^{-3} Standard deviation = 0.1232×10^{-3}

Coefficient of variation = 1.45%

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BIOGRAPHICAL SKETCH

Pramod Bhaurao Chemburkar was born September 3, 1932, at Bombay, India. In June, 1949, he graduated from Indian Education Society's Boys' High School receiving the Secondary School Certificate. In June, 1953, he received the degree of Bachelor of Science from the University of Bombay. In September, 1955, he received the degree of Bachelor of Pharmacy from Gujarat University. From 1955 until 1958 he served at the Lallubhai Motilal College of Pharmacy as a teaching assistant and also worked towards the degree of Master of Pharmacy which he received in June, 1958. He joined Indoco Remedies Limited, Bombay, and worked as Chief Chemist until January, 1962. He came to the United States in February, 1962 and enrolled in the Graduate School of the University of Florida. He worked as a teaching and research assistant in the College of Pharmacy, and also received a Graduate School Fellowship for the year 1964-65. He has pursued his work towards the degree of Doctor of Philosophy until the present time.

Pramod Bhaurao Chemburkar is married to the former Mrunalini Jayawant Bhatte and is the father of two sons, Yogen and Dipen. He is member of Rho Pi Phi, Professional Pharmacy Fraternity, and Rho Chi, Pharmacy Scholastic Honorary Society. He is the past president of the India Club at the University of Florida. Mr. Chemburkar will join Wyeth Laboratories, Philadelphia, Pennsylvania, upon completion of his studies.

This dissertation was prepared under the direction of the chairman of the candidate's supervisory committee and has been approved by all members of that committee. It was submitted to the Dean of the College of Pharmacy and to the Graduate Council, and was approved as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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